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☐	L23	L22 and combination	89
☐	L22	(EGFR)same(ErbB1)same(antibod?)	89
☐	L21	L20 and (combination)same(antibod?)	55
☐	L20	L18	87
☐	L19	L18 and epitope	44
☐	L18	L17 and (pharmaceutical)adj(composition)	87
☐	L17	L16 and combination	106
☐	L16	L15 and EGFR	108
☐	L15	(ErbB1)same(antibod?)	123
	DB=USPT; PLUR=YES; OP=OR		
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☐	L13	6342291.pn.	1
	DB=PGPB; PLUR=YES; OP=OR		
☐	L12	6342291.pn.	0
☐	L11	20060002920	1
☐	L10	20060002920A	0
☐	L9	20060002920A	0
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☐	L6	4968603.pn.	1
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☐	L5	EP-655924-A1.did.	0
	DB=DWPI; PLUR=YES; OP=OR		
☐	L4	655924	5
☐	L3	9400136	10
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=> s composition
L1 3421187 COMPOSITION

=> s k1 and antibod?
L2 3385 K1 AND ANTIBOD?

=> s l2 and combination
L3 144 L2 AND COMBINATION

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L6 3 DUP REMOVE L5 (4 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
95403469. PubMed ID: 7673253. Heregulin activation of extracellular acidification in mammary carcinoma cells is associated with expression of HER2 and HER3. Chan S D; Antoniucci D M; Fok K S; Alajoki M L; Harkins R N; Thompson S A; Wada H G. (Molecular Devices Corporation, Sunnyvale, California 94089, USA.) The Journal of biological chemistry, (1995 Sep 22) Vol. 270, No. 38, pp. 22608-13. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB HER2, the **erbB**-2/neu proto-oncogene product, is a 185-kDa transmembrane glycoprotein related to the epidermal growth factor receptor. Overexpression of HER2 was reported in several human

adenocarcinomas, including mammary and ovarian carcinomas. A family of glycoproteins, the heregulin/neu differentiation factors, was characterized and implicated as the ligands for HER2. Recently, it has been shown that HER2 alone is not sufficient to reconstitute high affinity heregulin receptors and that HER3 or HER4 may be the required components of the heregulin receptors on mammary carcinoma cells (Sliwkowski, M.X., Schaefer, G., Akita, R.W., Lofgren, J.A., Fitzpatrick, V.D., Nuijens, A., Fendly, B.M., Cerione, R.A., Vandlen, R.L., and Carraway, K.L., III (1994) J. Biol. Chemical 269, 14661-14665; Plowman, G.D., Green, J.M., Culouscou, J.-M., Carlton, G.W., Rothwell, V.M., and Buckley, W. (1993) Nature 366, 473-475). Using the Cytosensor to measure the extracellular acidification rate, we have examined the effects of recombinant human heregulin-alpha on three mammary carcinoma cell lines expressing HER2 (MDA-MB-453, SK-BR-3, and MCF-7), an ovarian carcinoma cell line expressing HER2 (SK-OV-3), and CHO-**K1** and 293-EBNA cells stably transfected with HER2. By reverse transcription polymerase chain reaction and Western blotting, we found that the breast cells also express HER3 and that the ovarian line co-expresses the HER4 message. A dramatic increase in the acidification rate was observed for the mammary carcinoma cells co-expressing high levels of HER2 and HER3. In contrast, the ovarian cells expressing high levels of HER2 and low levels of HER4 or CHO-**K1** and 293-EBNA cells expressing HER2 alone were not responsive to heregulin. When these same transfected cells were exposed to monoclonal anti-HER2 **antibody** followed by anti-IgG to cause aggregation of the HER2 molecules, an increase in the acidification rate was observed, indicating coupling of transfected HER2 to the signal transduction pathway. Transfection of HER2 into MCF-7 cells, on the other hand, gave 4-fold enhanced acidification responses. These data, together with the previously reported high affinity heregulin binding and activation of tyrosine phosphorylation in HER2 and HER3 co-transfected cells support the role of HER2 and HER3 as components of the heregulin receptor in breast cells.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

1995:254144 Document No. 122:47384 Keratinocyte growth factor receptor ligands induce transforming growth factor α expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz, Andrzej A.; Cheng, Christina; Denning, Mitchell F.; Dempsey, Peter J.; Coffey, Robert J., Jr.; Yuspa, Stuart H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, MD, 20892, USA). Cell Growth & Differentiation, 5(12), 1283-92 (English) 1994. CODEN: CGDIE7. ISSN: 1044-9523. Publisher: American Association for Cancer Research.

AB EGF receptor (EGFR) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor α (TGFα) and EGF elicit distinctive changes in keratin expression: Ca2+-mediated induction of the differentiation-specific keratins **K1** and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., 1993). We have evaluated several addnl. growth factors to determine the specificity of this response for EGFR ligands. TGFα, keratinocyte growth factor (KGF), and acidic FGF (aFGF), but not basic FGF (bFGF) or IGF-I, block Ca2+-mediated expression of **K1** while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGFα/EGFR pathway is an intermediary in signaling through the KGFR. TGFα mRNA was increased in cells treated with KGF, aFGF, or TGFα but not bFGF or IGF-I. Similar changes were detected at the protein level; TGFα in conditioned medium (CM) from control, KGF-, TGFα-, and aFGF-treated cultures was 54, 365, 146, and 120 pg/mL, resp. KGF and TGFα also increased expression of cell-associated TGFα measured in keratinocyte lysates. KGF increased TGFα secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with

neutralizing **antibodies** or both TGFα and KGF, but not KGF **antibody** alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGFα. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGFα resulted in EGFR autophosphorylation. Furthermore, after .apprx.24 h, KGF as well as TGFα induced EGFR down-regulation based on Western blot anal. and 125I-EGF binding. Induction of TGFα in KGF-treated keratinocytes, coupled to activation and down-modulation of the EGFR, suggests that TGFα may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L6 ANSWER 3 OF 3 MEDLINE on STN
92290622. PubMed ID: 1351045. Frequent expression of the tumor antigen CAK1 in squamous-cell carcinomas. Chang K; Pastan I; Willingham M C. (Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) International journal of cancer. Journal international du cancer, (1992 Jun 19) Vol. 51, No. 4, pp. 548-54. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB **K1** is a murine monoclonal **antibody** (MAb) derived from a hybridoma generated by the fusion of splenocytes of BALB/c mice immunized with a human ovarian tumor cell line, OVCAR-3. This **antibody** reacts strongly with epithelial ovarian tumors and mesotheliomas. The antigen recognized by MAb **K1**, designated CAK1, has recently been characterized as a 40-kDa protein probably anchored to the cell surface by glycosyl-phosphatidylinositol. Using immunoperoxidase histochemical methods, we examined 37 squamous-cell carcinoma (SqCC) samples from cervix, lung, esophagus and other origins, and 12 normal squamous epithelia of the cervix and esophagus for their reactivity with MAb **K1**. Of the SqCC specimens, 81% showed **K1** reactivity with variable intensity, but none of 12 normal tissue samples of squamous epithelia did so. Two patterns of CAK1 expression in tumor samples were found, i.e., a heterogeneous pattern with strong intensity, and a homogeneous pattern with weak intensity. Three carcinomas in situ of the larynx, vulva and esophagus were moderately positive with **K1**, suggesting that CAK1 antigen may occur in the early stage of carcinogenesis of SqCC. The expression of CAK1 was also compared with expression of CA125, HER-2/neu, p53 and P-glycoprotein, and MAb **K1** was found to react most consistently with SqCC. Since **K1** reacts with a majority of cervical and esophageal carcinomas but has no detectable reactivity in normal epithelia of the cervix uteri and esophagus, MAb **K1** could be of value as a reagent to help distinguish between normal and neoplastic cells on sections as well as in cytological samples.

=> s l3 and EGFR
L7 0 L3 AND EGFR

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L9 7 DUP REMOVE L8 (6 DUPLICATES REMOVED)

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L9 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2006718900. PubMed ID: 16886908. Selection and characterization of an internalizing epidermal-growth-factor-receptor **antibody.** Zhao Xiaorong; Dai Wentao; Cao Limin; Zhu Huifen; Yu Yihan; Ye Qing; Wang Min; Dai Wei; Lei Ping; Shen Guanxin. (Laboratory of Molecular and Immuno-Pharmacology, Department of Immunology Tongji Medical College,

Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China.) Biotechnology and applied biochemistry, (2007 Jan) Vol. 46, No. Pt 1, pp. 27-33. Journal code: 8609465. E-ISSN: 1470-8744. Pub. country: England: United Kingdom. Language: English.

AB **Antibody**-therapeutic agent conjugates to be delivered directly into the cytosol of tumour cells is required for many target-based therapeutic strategies. For this work, a large non-immune phage-display library was used to select internalizing scFv (single chain variable fragment) directed against **EGFR** (epidermal growth factor receptor), a tyrosine kinase receptor that is overexpressed in a wide range of tumour cells. The CHO-**EGFR**-GFP1 (where CHO is Chinese-hamster ovary) cell line, a transfected cell line expressing **EGFR**-GFP (green fluorescent protein) fusion protein on membranes, and the untransfected cell line CHO-**K1** were used as **EGFR** -positive cells and -negative cells respectively in the subtractive selection procedure. A novel human anti-**EGFR** scFv (F4-scFv) was isolated. F4-scFv bound native **EGFR**-bearing cell lines and could be internalized, but did not bind **EGFR**-negative cell lines. The K(D) value of F4-scFv was 472 nM as determined on A431 cells. F4-scFv could be used to target therapeutic agents into tumour cells and was expected to be non-immunogenic in humans. Use of a transfected cell line expressing GFP-tagged receptors allows selection and characterization of **antibodies** to native receptors without the need for protein expression and purification, significantly speeding up the generation of targeting **antibodies.**

L9 ANSWER 2 OF 7 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:297056 Document No.: PREV200600297498. Directed evolution of the epidermal growth factor receptor extracellular domain for expression in yeast. Kim, Yong-Sung; Bhandari, Rashna; Cochran, Jennifer R.; Kuriyan, John; Wittrup, K. Dane [Reprint Author]. MIT, Div Biol Engn, 400 Main St Bldg 66-552, Cambridge, MA 02139 USA. wittrup@mit.edu. Proteins Structure Function and Bioinformatics, (MAR 1 2006) Vol. 62, No. 4, pp. 1026-1035. CODEN: PSFGEY. ISSN: 0887-3585. Language: English.

AB The extracellular domain of epidermal growth factor receptor (**EGFR** -ECD) has been engineered through directed evolution and yeast surface display using conformationally-specific monoclonal **antibodies** (mAbs) as screening probes for proper folding and functional expression in Saccharomyces cerevisiae. An **EGFR** mutant with four amino acid changes exhibited binding to the conformationally-specific mAbs and human epidermal growth factor, and showed increased soluble secretion efficiency compared with wild-type **EGFR.** Full-length **EGFR** containing the mutant **EGFR**-ECD was functional, as assayed by EGF-dependent autophosphorylation and intracellular MAPK signaling in mammalian cells, and was expressed and localized at the plasma membrane in yeast. This approach should enable engineering of other complex mammalian receptor glycoproteins in yeast for genetic, structural, and biophysical studies.

L9 ANSWER 3 OF 7 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2006251624 EMBASE The efficacy of alginate encapsulated CHO-**K1** single chain-TRAIL producer cells in the treatment of brain tumors. Kuijlen J.M.A.; de Haan B.J.; Helfrich W.; de Boer J.-F.; Samplonius D.; Mooij J.J.A.; de Vos P.. J.M.A. Kuijlen, Department of Neurosurgery, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, Netherlands. j.m.a.kuijlen@nchir.umcg.nl. Journal of Neuro-Oncology Vol. 78, No. 1, pp. 31-39 2006.
Refs: 23.
ISSN: 0167-594X. E-ISSN: 1573-7373. CODEN: JNODD2
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060615. Last Updated on STN: 20060615

AB Object: Patients with astrocytic tumors in the central nervous system (CNS) have low survival rates despite surgery and radiotherapy. Innovative therapies and strategies must be developed to prolong survival

of these patients. The alginate microencapsulation method, used to continuously release a certain cytotoxic agent in the vicinity of the tumor, is such a novel therapeutic strategy. The biological functionality of the apoptosis inducing scFv425:sTRAIL protein, which was released through the microencapsulation method, was studied in vitro. Analysis of the intracerebral biocompatibility of alginate capsules was performed by implantation of empty alginate capsules in the brain of mice. Method: Chinese Hamster Ovary cells (CHO-**K1**) were recombinantly engineered to produce the single chain anti-**EGFR**-sTRAIL protein (scFv425:sTRAIL). The CHO-**K1** producer cells were encapsulated in an alginate capsule with a semi-permeable membrane through which the scFv425:sTRAIL protein could be released. Results: In vitro studies show maintained biological functionality of the released scFv425:sTRAIL protein. There was no immunological tissue response detectable after intracerebral implantation of the alginate capsules in mice brains. Conclusion: Biological functionality of the produced scFv425:sTRAIL protein is maintained and intracerebral biocompatibility of the capsules is warranted. Alginate encapsulation of CHO-**K1** - scFv425:sTRAIL - producer cells and subsequently their intracerebral implantation is technically feasible. This study justifies further in vivo experiments. .COPYRGT. Springer Science+Business Media, Inc. 2006.

L9 ANSWER 4 OF 7 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2001:331622 The Genuine Article (R) Number: 422QK. Proliferation and differentiation of the keratinocytes in hyperplastic epidermis overlying dermatofibroma - Immunohistochemical characterization.. Han K H; Huh C H; Cho K H (Reprint). Seoul Natl Univ Hosp, Dept Dermatol, Chongno Gu, 28 Yongon Dong, Seoul 110744, South Korea (Reprint); Seoul Natl Univ Hosp, Clin Res Inst, Lab Cutaneous Aging Res, Chongno Gu, Seoul 110744, South Korea; Seoul Natl Univ, Coll Med, Dept Dermatol, Seoul 110744, South Korea . AMERICAN JOURNAL OF DERMATOPATHOLOGY (APR 2001) Vol. 23, No. 2, pp. 90-98. ISSN: 0193-1091. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Epidermal changes overlying dermatofibromas (DFs) have been described as ranging from psoriasiform simple hyperplasia to basaloid hyperplasia sometimes morphologically indistinguishable from superficial basal cell carcinoma (BCC). To characterize epidelmal hyperplasia overlying DFs and to determine its association with the disease process, we examined 30 cases of DF showing hyperplastic epidermis. We used nine immunohistochemical markers associated with keratinocyte proliferation or differentiation. In DFs, the dermal metallothionein (MT) expression and immunophenotypic changes with regard to epidermal differentiation varied depending on the stage of lesional evolution of the DFs. Immunostaining for epidermal growth factor receptor (**EGFR**), MT, and keratin 6 (K6) increased in simple hyperplastic epidermis (SHE) overlying DFs (n = 11), whereas it gradually diminished in basaloid hyperplastic epidermis (BHE) overlying DFs (n = 19). In SHE, there was a significant increase in K14 expression. Among 19 BHE: cases, 12 showed premature expression of involucrin and delayed appearance of **K1** along with aberrant expression of K14. Conversely, the remaining 7 BHE cases showed a pattern of involucrin and **K1** similar to that of normal skin coinciding with decreased or absent dermal M7 expression. Loricrin and filaggrin expression in all DFs was the same as that of normal skin. Based on the sparse positivity of Ki-67 in the hyperplastic epidermis overlying DFs, we found that the biologic ability of BHE and SHE was not apparent in the hyperproliferative state observed in psoriasis and BCC. Thee results suggest that the dermal fibrohistiocytic process may trigger the induction of SHE overlying DFs by an unknown mechanism and then mediate both the abnormal keratinocyte differentiation and the transformation of SHE to BHE through the evolution of the dermal lesions.

L9 ANSWER 5 OF 7 MEDLINE on STN

97384952. PubMed ID: 9242447. Targeted disruption of the epidermal growth

factor receptor impairs growth of squamous papillomas expressing the v-ras(Ha) oncogene but does not block in vitro keratinocyte responses to oncogenic ras. Dlugosz A A; Hansen L; Cheng C; Alexander N; Denning M F; Threadgill D W; Magnuson T; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892, USA.) Cancer research, (1997 Aug 1) Vol. 57, No. 15, pp. 3180-8. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB We have assessed the role of epidermal growth factor receptor (**EGFR**) signaling in biological responses to the v-ras(Ha) oncogene using primary keratinocytes from **Egfr** -/- mice and wild-type littermates. On the basis of several criteria, **Egfr** -/- keratinocytes were unresponsive to either acute or chronic exposure to several **EGFR** ligands but were stimulated to proliferate in response to several other mitogens. Although conditioned medium from primary keratinocytes transduced with v-ras(Ha) retrovirus (v-ras(Ha) keratinocytes) was a potent mitogen for wild-type but not **Egfr** -/- keratinocytes, v-ras(Ha) transduction of primary keratinocytes of either genotype resulted in a strong mitogenic response, arguing against an obligatory role for **EGFR** activation in v-ras(Ha)-mediated stimulation of keratinocyte proliferation. Infection with high-titer v-ras(Ha) retrovirus altered the keratin expression pattern in keratinocytes of both genotypes, suppressing differentiation-specific keratins **K1** and K10 while activating aberrant expression of K8 and K18. In wild-type but not **Egfr** -/- cultures, **K1** and K10 were also suppressed following infection at lower retroviral titers, presumably as a result of paracrine **EGFR** activation on uninfected cells present in these cultures. Squamous papillomas produced by grafting **Egfr** -/- v-ras(Ha) keratinocytes onto nude mice were only 21% of the size of wild-type v-ras(Ha) tumors, and a striking redistribution of S-phase cells was detected by immunostaining for bromodeoxyuridine. In **Egfr** -/- v-ras(Ha) papillomas, the fraction of total labeled nuclei detected in suprabasal layers was increased from 19 to 39%. In contrast, the basal layer labeling index of **Egfr** -/- papillomas was reduced to 34%, compared to 43% in wild-type tumors. Our results indicate that, although autocrine **EGFR** signaling is not required for keratinocyte responses to oncogenic ras in culture or benign tumor formation in nude mouse grafts, disruption of this pathway impairs growth of v-ras(Ha) papillomas by a mechanism that may involve alterations in keratinocyte cell cycle progression and/or migration in vivo.

L9 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 3

95210161. PubMed ID: 7535082. Keratinocyte growth factor receptor ligands induce transforming growth factor alpha expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz A A; Cheng C; Denning M F; Dempsey P J; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892.) Cell growth & differentiation : the molecular biology journal of the American Association for Cancer Research, (1994 Dec) Vol. 5, No. 12, pp. 1283-92. Journal code: 9100024. ISSN: 1044-9523. Pub. country: United States. Language: English.

AB Epidermal growth factor receptor (**EGFR**) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor alpha (TGF alpha) and EGF elicit distinctive changes in keratin expression: Ca(2+)-mediated induction of the differentiation-specific keratins **K1** and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., Cell Growth, & Differ., 4: 317-327, 1993). We have evaluated several additional growth factors to determine the specificity of this response for **EGFR** ligands. TGF alpha, keratinocyte growth factor (KGF), and acidic fibroblast growth factor (aFGF), but not basic fibroblast growth factor (bFGF) or insulin-like

growth factor type I, block Ca(2+)-mediated expression of **K1** while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGF alpha/ **EGFR** pathway is an intermediary in signaling through the KGFR. TGF alpha mRNA was increased in cells treated with KGF, aFGF, or TGF alpha but not bFGF or insulin-like growth factor type I. Similar changes were detected at the protein level; TGF alpha in conditioned medium (CM) from control, KGF-, TGF alpha-, and aFGF-treated cultures was 54 (+/- 8, SEM), 365 (+/- 50), 146 (+/- 20), and 120 (+/- 50) pg/ml, respectively. KGF and TGF alpha also increased expression of cell-associated TGF alpha measured in keratinocyte lysates. KGF increased TGF alpha secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with neutralizing **antibodies** to both TGF alpha and KGF, but not KGF **antibody** alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGF alpha. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGF alpha resulted in **EGFR** autophosphorylation. Furthermore, after approximately 24 h, KGF as well as TGF alpha induced **EGFR** down-regulation based on Western blot analysis and 125I-EGF binding. Induction of TGF alpha in KGF-treated keratinocytes, coupled to activation and down-modulation of the **EGFR**, suggests that TGF alpha may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L9 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
1993:6287 Document No.: PREV199395006287. Relationships between Ki-67 labelling index, amplification of the epidermal growth factor receptor gene, and prognosis in human glioblastomas. Torp, S. H. [Reprint author]; Helseth, E.; Dalen, A.; Unsgaard, G.. Inst. Cancer Res., Med. Technical Cancer, N-7005 Trondheim, Norway. Acta Neurochirurgica, (1992) Vol. 117, No. 3-4, pp. 182-186.
CODEN: ACNUA5. ISSN: 0001-6268. Language: English.

AB The aim of this study was to determine possible relationships between Ki-67 labelling index (Ki-67 LI), amplification of the epidermal growth factor receptor (**EGFR**) gene, and prognosis in human glioblastomas. Ki-67 LI was determined on cryosections of biopsy specimens of 20 human glioblastomas with a mouse antihuman Ki-67 monoclonal **antibody.** Amplification of the **EGFR** gene was determined by slot blot and Southern blot analyses of DNA extracted from the tumour biopsies. The Ki-67 LI was higher in the glioblastoma group with **EGFR** gene amplification (8 tumours, median value of Ki-67 LI 4.2, range 0.4-24.6) than in those without **EGFR** gene amplification (12 tumours, median value of Ki-67 LI 0.8 range 0.2-11.8) (0.05 p lt 0.01). The glioblastoma patients with Ki-67 LI gt 1.5 (10 tumours) had a statistically significant shorter survival than those with Ki-67 LI KAPPA 1.5 (10 tumours) (p lt 0.05). The glioblastoma patients with **EGFR** gene amplification, lived shorter time than those without **EGFR** gene amplification (p gt 0.05).

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L10    2980692 ANTIBOD?

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L12         151 L11 AND EGFR

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L13 39 L12 AND COMBINATION

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L14 15 DUP REMOVE L13 (24 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:303341 Document No.: PREV200700308469. The **combination** of lapatinib (GW572016F) and agents targeting the insulin-like growth factor I receptor results in synergistic tumor cell growth inhibition and induction of apoptosis. Rusnak, David W. [Reprint Author]; Kumar, Rakesh; Gilmer, Tona M.. GlaxoSmithKline Inc, Res Triangle Pk, NC USA. Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2007) Vol. 48, pp. 1357.
Meeting Info.: 98th Annual Meeting of the American-Association-for-Cancer-Research. Los Angeles, CA, USA. April 14 -18, 2007. Amer Assoc Canc Res.
ISSN: 0197-016X. Language: English.

L14 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1
2007075608. PubMed ID: 17208435. Dual inhibition of **ErbB1** (**EGFR**/HER1) and ErbB2 (HER2/neu). Reid Alison; Vidal Laura; Shaw Heather; de Bono Johann. (Royal Marsden Hospital, The Institute of Cancer Research, Centre for Cancer Therapeutics, Downs Road, Sutton, Surrey SM2 5PT, UK.) European journal of cancer (Oxford, England : 1990), (2007 Feb) Vol. 43, No. 3, pp. 481-9. Electronic Publication: 2007-01-08. Ref: 82. Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.
AB Targeting of epidermal growth factor receptor (**EGFR**) and HER2 is a proven anti-cancer strategy. However, heterodimerisation, compensatory 'crosstalk' and redundancy exist in the ErbB network, and there is therefore a sound scientific rationale for dual inhibition of **EGFR** and HER2. Trials of approved agents in **combination**, for example trastuzumab and cetuximab, are underway. There is also a new generation of small molecule tyrosine kinase inhibitors (TKIs) and monoclonal **antibodies** (mABs) that target two or more ErbB receptors. Lapatinib, a TKI of **EGFR** and HER2, has shown clinical benefit in trastuzumab refractory breast cancer and is poised for FDA approval. Other agents include BIBW-2992 and HKI-272, irreversible TKIs of **EGFR** and HER2, and pertuzumab, a heterodimerisation inhibitor of **EGFR** and HER2.

L14 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
2007098583. PubMed ID: 16738850. Efficient inhibition of **EGFR** signaling and of tumour growth by antagonistic anti-EFGR Nanobodies. Roovers Rob C; Laeremans Toon; Huang Lieven; De Taeye Severine; Verkleij Arie J; Revets Hilde; de Haard Hans J; van Bergen en Henegouwen Paul M P. (Department of Molecular Cell Biology, Institute of Biomembranes, Utrecht University, Padualaan 8, CH-3584 Utrecht, The Netherlands.) Cancer immunology, immunotherapy : CII, (2007 Mar) Vol. 56, No. 3, pp. 303-317. Journal code: 8605732. ISSN: 0340-7004. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB The development of a number of different solid tumours is associated with over-expression of **ErbB1**, or the epidermal growth factor receptor (**EGFR**), and this over-expression is often correlated with poor prognosis of patients. Therefore, this receptor tyrosine kinase is considered to be an attractive target for **antibody**-based therapy. Indeed, **antibodies** to the **EGFR** have already proven their value for the treatment of several solid tumours, especially in **combination** with chemotherapeutic treatment regimens. Variable domains of camelid heavy chain-only **antibodies** (called Nanobodies) have superior properties compared with classical

antibodies in that they are small, very stable, easy to produce in large quantities and easy to re-format into multi-valent or multi-specific proteins. Furthermore, they can specifically be selected for a desired function by phage **antibody** display. In this report, we describe the successful selection and the characterisation of antagonistic anti-**EGFR** Nanobodies. By using a functional selection strategy, Nanobodies that specifically competed for EGF binding to the **EGFR** were isolated from "immune" phage Nanobody repertoires. The selected **antibody** fragments were found to efficiently inhibit EGF binding to the **EGFR** without acting as receptor agonists themselves. In addition, they blocked EGF-mediated signalling and EGF-induced cell proliferation. In an in vivo murine xenograft model, the Nanobodies were effective in delaying the outgrowth of A431-derived solid tumours. This is the first report describing the successful use of untagged Nanobodies for the in vivo treatment of solid tumours. The results show that functional phage **antibody** selection, coupled to the rational design of Nanobodies, permits the rapid development of novel anti-cancer **antibody**-based therapeutics.

L14 ANSWER 4 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007012849 EMBASE HER-2 and NF-κB as the targets for therapy-resistant breast cancer. Ahmed K.M.; Cao N.; Li J.J.. Dr. J.J. Li, 1279 Civil Engineering Building, 550 Stadium Mall Drive, West Lafayette, IN 47907, United States. jjli@purdue.edu. Anticancer Research Vol. 26, No. 6 B, pp. 4235-4243 2006.
Refs: 106.
ISSN: 0250-7005. CODEN: ANTRD4
Pub. Country: Greece. Language: English. Summary Language: English.
Entered STN: 20070130. Last Updated on STN: 20070130

AB HER-2 (also called ErbB2 or Neu) tyrosine kinase, one of the four members of ErbB receptor family (**ErbB1**, i.e., **EGFR**, ErbB2, ErbB3 and ErbB4), plays a critical role in the control of diverse cellular functions involved in differentiation, proliferation, migration and cell survival via multiple signal transduction pathways. Overexpression of HER-2, observed in HER-2-positive breast cancer patients, is believed to cause the tumor resistance to an array of anti-cancer agents and poor prognosis. Although HER-2 **antibodies** have shown growth inhibitory effects, more efficient molecular targets against HER-2-mediated tumor resistance need to be developed. The molecular mechanisms underlying HER-2-mediated tumor resistance, especially the connections between HER-2 and therapy-resistant signaling networks, need to be further investigated. NF-KB, a key stress transcription factor that can initiate a pro-survival network, was found to be activated in many cancer cells overexpressing HER-2 and to be responsible for the radiation resistance in HER-2 transfected breast cancer cells. Recent findings in literature and data from this laboratory suggest a possible co-operation between HER-2 and NF-κB in signaling tumor resistance to radiotherapy. This review will discuss the mechanisms of HER-2 mediated NF-κB signaling pathway and potential target for therapeutic intervention.

L14 ANSWER 5 OF 15 MEDLINE on STN DUPLICATE 3

2006581555. PubMed ID: 16858684. Peptabody-EGF: a novel apoptosis inducer targeting **ErbB1** receptor overexpressing cancer cells. Fattah Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R; Mach Jean Pierre; Deperthes David. (Department of Urology, Urology Research Unit, CHUV, Epalinges, Switzerland.) International journal of cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10, pp. 2455-63. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The epidermal growth factor receptor (**EGFR**) plays a central role in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial

malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of **EGFR** represents a very promising challenge in oncology, and **antibodies** raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such **antibodies**, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or **combinations** thereof. We report here the development of an alternative high affinity molecule that is directed against **EGFR.** Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of **EGFR.** Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing **EGFR.** However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal **EGFR antibody** Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on **EGFR** overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-**EGFR** therapy.

L14 ANSWER 6 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006266133 EMBASE EGF receptor mutations in lung cancer: From humans to mice and maybe back to humans. Arteaga C.L.. C.L. Arteaga, Departments of Medicine and Cancer Biology, Breast Cancer Research Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, United States. carlos.arteaga@vanderbilt.edu. Cancer Cell Vol. 9, No. 6, pp. 421-423 13 Jun 2006.
Refs: 23.
ISSN: 1535-6108. CODEN: CCAECI
S 1535-6108(06)00151-6. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060706. Last Updated on STN: 20060706

AB Deletions in exon 19 and nucleotide substitutions in exon 21 are the most common mutations of the **EGFR** (**ErbB1**) in NSCLC. These mutations endow the receptor with constitutive kinase activity. Most tumors expressing these mutants respond well to **EGFR** tyrosine kinase inhibitors, suggesting that they are dependent on mutant **EGFR** signaling. Two groups developed transgenic mice in which expression of these mutants is temporally induced in mouse lung. Mice expressing **EGFR** mutants develop bronchioloalveolar cancer and lung adenocarcinoma, which are highly sensitive to **EGFR** inhibitors. These mouse models provide important opportunities for studying the biology of NSCLC and the refinement of anti-**EGFR** therapies.

L14 ANSWER 7 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006374473 EMBASE The complexity of targeting **EGFR** signalling in cancer: From expression to turnover. Sebastian S.; Settleman J.; Reshkin S.J.; Azzariti A.; Bellizzi A.; Paradiso A.. A. Paradiso, Clinical Experimental Oncology Laboratory, National Cancer Institute, Via Amendola, 209, 70126 Bari, Italy. a.paradiso@oncologico.bari.it. Biochimica et Biophysica Acta - Reviews on Cancer Vol. 1766, No. 1, pp. 120-139 2006.
Refs: 250.
ISSN: 0304-419X. CODEN: BBACEU
S 0304-419X(06)00032-1. Pub. Country: Netherlands. Language: English.

Summary Language: English.
Entered STN: 20060824. Last Updated on STN: 20060824

AB The epidermal growth factor receptor (**ErbB1** or **EGFR**) has been found to be altered in a variety of human cancers. A number of agents targeting these receptors, including specific **antibodies** directed against the ligand-binding domain of the receptor and small molecules that inhibit kinase activity are either in clinical trials or are already approved for clinical treatment. However, identifying patients that are likely to respond to such treatments has been challenging. As a consequence, it still remains important to identify additional alterations of the tumor cell that contribute to the response to **EGFR**-targeted agents. While **EGFR**-mediated signalling pathways have been well established, there is still a rather limited understanding of how intracellular protein-protein interactions, ubiquitination, endocytosis and subsequent degradation of **EGFR** contribute to the determination of sensitivity to **EGFR** targeting agents and are emerging areas of investigation. This review primarily focuses on the basic signal transduction pathways mediated through activated membrane bound and/or endosomal **EGFR** and emphasizes the need to co-target additional proteins that function either upstream or downstream of **EGFR** to improve cancer therapy.

L14 ANSWER 8 OF 15 SCISEARCH

2005:579387 The Genuine Article (R) Number: 930JI. Clinical applications for targeted therapy in bladder cancer. Adam L; Kassouf W; Dinney C P N (Reprint). Univ Texas, MD Anderson Canc Ctr, Dept Urol, 1515 Holcombe Blvd, Unit 1373, Houston, TX 77030 USA (Reprint); Univ Texas, MD Anderson Canc Ctr, Dept Urol, Houston, TX 77030 USA; Univ Texas, MD Anderson Canc Ctr, Dept Canc Biol, Houston, TX 77030 USA. cdinney@mdanderson.org. UROLOGIC CLINICS OF NORTH AMERICA (MAY 2005) Vol. 32, No. 2, pp. 239-+. ISSN: 0094-0143. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Transitional cell carcinoma (TCC) of the bladder is the fourth most common solid-tumor malignancy in men in the United States. Approximately 17,060 men in the United States died from TCC of the bladder in 2004; most of the deaths were due to metastatic disease [1]. Metastatic TCC is usually treated with systemic chemotherapy, including regimens such as M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) (2-4]. However, despite systemic chemotherapy with even the most effective regimens, most patients with distant metastatic bladder cancer die of the disease after a median survival duration of 18 months [3,4]. Although considerable efforts have been made to escalate the dose of MNAC, to modulate the components of the regimens, and to use novel **combination** regimens that include active agents such as paclitaxel, gemcitabine, and ifosfamide, there has been no improvement in survival [5-10]. Although some of these newer regimens produce fewer toxic side effects than MNAC, there is yet no compelling evidence that they improve patient survival. In general, the treatment of metastatic TCC of the bladder by classic cytotoxic chemotherapy has reached a therapeutic plateau. Despite high rates of response to treatment, the disease is generally incurable. However, it is clear that cytotoxic chemotherapy has provided significant palliation for many patients, and has resulted in improved outcome, probability for cure, or both in the adjuvant setting of microscopic metastatic disease.

Although chemotherapy is still an important component of combined therapy, the need for more effective treatment options exists. Fortunately, an improved understanding of the biology of malignancy is finally facilitating the design of novel therapeutic approaches to battle cancer. Urothelial transformation involves several cellular events including the deregulation of cellcycle and apoptotic pathways via mutation or altered expression of p53, p21/WAF-1, pRB, p27, and INK4A

(p16). Progression of urothelial carcinoma has also been related to various members of the erbB family, vascular epidermal growth factor (VEGF), nerve factor-kappa B (NF kappa B), Akt, PTEN, and cyclooxygenase/2 (COX-2) [11]. All of these molecules are potential targets for novel therapies. The focus of this article is the aberrant signal transduction of members of the erbB family (ie, epidermal growth factor receptor [**EGFR**], and human epidermal growth factor receptors [HER]-2, -3, and -4) in TCC of the bladder. **EGFR** was sequenced and cloned by Ullrich in 1984 [12]. **EGFR**, HER1, or c-**erbB1**, is the prototype of the type I receptor tyrosine kinase (RTK) family, which also includes HER2 (cerbB2), HER3 (c-erbB-3), and HER4 (c-erbB-4) [13-15]. **EGFR** family members transmit the biologic effects of the EGF family of ligands, which includes EGF, transforming growth factor-alpha (TGF alpha), amphiregulin, heparin-binding (HB)-EGF, betacellulin, and epiregulin. Ligand binding induces the formation of homodimers or heterodimers between **EGFR** and other members of this family, autophosphorylation of tyrosine residues in its intracellular domain, and activation of downstream signaling pathways [13-15]. These phosphotyrosines, in turn, phosphorylate other intracellular proteins that contain src homologous domains (SH2 and SH3), such as ras-associated GTPase activating protein, phosphatidylinositol3-kinase, and phospholipase C gamma. The downstream signaling pathways activated by these intracellular proteins include the ras/raf MAPKinase, phosphatidylinositol-3-kinase, and protein kinase C pathways, which ultimately lead to increased nuclear transcription and subsequent cellular proliferation [15,16]. Overexpression of **EGFR** alone or accompanied by production of one or more of its ligands, such as TGF alpha, has been reported in a range of human malignancies and is often associated with poor prognosis [16,17]. Overexpression of **EGFR** in bladder cancer has been widely reported [1823]. The reports suggest the presence of **erbB1** in 23% to 100% of TCC samples. Several studies have shown that **EGFR** is positively associated with advanced tumor stage, tumor progression, and poor clinical outcome [24]. Immunohistochemical analyses suggest that rather than actual overexpression of **erbB1** in TCC is the actual change in the distribution of the molecule, from basal layer in normal urothelium to all layers in premalignant or malignant urotheliums [25,26]. Other studies have demonstrated that expression of **erbB1** and of erbB2 is downregulated in TCC compared with the expression in normal urothelium [27]. Still other studies have demonstrated erbB3 in 20% to 56% and erbB4 in 11% to 30% of cases of TCC, but reduced expression of erbB3 and erbB4 in TCC compared with normal tissues [27]. Statistical analyses of erbB expression patterns and clinical parameters have resulted in varying conclusions about the prognostic significance of erbB expression in TCC [27-32].

However, in patients with muscle-invasive TCC of the bladder, a retrospective immunohistochemical study has shown erbB2 overexpression to be a independent predictor of reduced cancer-specific survival [33]. In contrast, another prospective study found that erbB2 overexpression in the context of paclitaxel-based chemotherapy significantly decreased the risk of death [34]. On the basis of discovery of variant isoforms of the erbB family members, a series of studies was initiated that focused on acquiring quantitative information about erbB status, which was considered critical for selecting patients for erbB inhibitor therapies, and for evaluating the potential use of erbBs as prognostic indicators for patients with cancer. A report by Juntilla et al [35] describing specific erbB4 cytoplasmic or juxtamembrane isoforms overexpressed in TCC compared with its expression in interstitial cystitis or normal bladder, is an example of such finding. Thus, preclinical evidence about the expression levels of specific erbBs in TCC tissues, although controversial at the moment, may be verified through a more refined investigation. Several erbB I variants, somatic mutations, deletions, or truncations have been described for **erbB1** in epithelial cancers, including lung, colon, and breast cancers [36-39]. For example, the erbBvIII variant, which lacks the extracellular domain, has been shown to be specifically

expressed in tumor tissues rather than in normal, adjacent tissues and to activate aberrant signaling pathways relevant for **EGFR**-targeted therapy [40,41]. However, there currently are no studies investigating this aspect in bladder cancer.

L14 ANSWER 9 OF 15 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:387361 The Genuine Article (R) Number: 912JF. Characterization of HER1 (c-**erbB1**) status in locally advanced breast cancer using fluorescence in situ hybridization and immunohistochemistry. Corzo C (Reprint); Tusquets I; Salido M; Corominas J M; Bellet M; Suarez M; Baro T; Fabregat X; Serrano S; Sole F. Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, Pg Maritim 25-29, ES-08003 Barcelona, Spain (Reprint); Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, ES-08003 Barcelona, Spain; Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Med Oncol Serv, ES-08003 Barcelona, Spain; Univ Autonoma Barcelona, Dept Biol Cellular Fisiol & Immunol, E-08193 Barcelona, Spain. E0062@imas.imim.es. TUMOR BIOLOGY (2005) Vol. 26, No. 1, pp. 25-30. ISSN: 1010-4283. Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Epidermal growth factor receptor (**EGFR**) is a 170-kDa transmembrane glycoprotein encoded by the HER1 protooncogene, located at 7p12. This receptor is related to the pathogenesis of breast cancer. The aim of this study was to analyze the status of HER1 using fluorescence in situ hybridization (FISH) and immunohistochemistry in a series of 48 patients with locally advanced breast cancer (LABC). Before neoadjuvant chemotherapy, core biopsies were taken from patients with LABC and were processed into paraffin blocks. Biopsies were then studied using FISH with a HER1 probe (Vysis, Downers Grove, Ill., USA). They were also analyzed immunohistochemically using two different **EGFR** **antibodies** from DakoCytomation (Denmark, A/S) and from Zymed (San Francisco, Calif., USA). HER1 amplifications were not found, although 31% of the cases presented aneusomy of chromosome 7. Only 2 cases presented **EGFR** expression. LABC presented a low level of **EGFR** expression. HER1 amplification was not present in LABC, although the polysomy of chromosome 7 was a common finding. Copyright (C) 2005 S. Karger AG, Basel.

L14 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2004:404840 Document No. 142:129837 Anti-**EGFR**-mediated radiosensitization as a result of augmented **EGFR** expression. Bonner, James A.; Buchsbaum, Donald J.; Russo, Suzanne M.; Fiveash, John B.; Trummell, Hoa Q.; Curiel, David T.; Raisch, Kevin P. (Department of Radiation Oncology, Univ. Alabama Sch Med., Birmingham, AL, USA). International Journal of Radiation Oncology, Biology, Physics, 59(2, Suppl.), 2-10 (English) 2004. CODEN: IOBPD3. ISSN: 0360-3016. Publisher: Elsevier Science Inc..

AB Elevated epidermal growth factor receptor (**EGFR**) expression has correlated with a poor prognosis after standard treatment of several malignancies. However, it is not clear whether the absolute level of **EGFR** expression affects the radiosensitizing properties of anti-**EGFR** treatments. A better understanding of this question would be helpful for the design of protocols that deliver these treatments. To explore this question, cells (LS174T) that did not display inherent anti-**EGFR** treatment-induced radiosensitization were selected for studies that could potentially enhance **EGFR** expression. Human colon carcinoma cells (LS174T), which did not show radiosensitization by anti-**EGFR** treatments, were employed for these studies. (Also, these cells were not responsive to the antiproliferative effects of anti-**EGFR** treatment.). Using standard transfection techniques (eukaryotic expression vector) as well as an adenoviral construct to enhance **EGFR** expression, LS174T cells were transduced in a manner that resulted in enhanced expression of **EGFR**. Subsequently, standard

proliferation studies were performed to test the radiosensitizing properties of anti-**EGFR** treatment (an anti-**EGFR** monoclonal **antibody**: IMC-C225). Studies were undertaken to stably transfect LS174T cells with **EGFR**. The stable transfectants, LS174T.**EGFR** cells, were responsive to the antiproliferative effects of anti-**EGFR** treatment, in contrast to the parent LS174T cells. Similar results were demonstrated when the cells were infected with AdEGFR. Addnl., the LS174T.**EGFR** cells were responsive to the radiosensitizing properties of anti-**EGFR** treatment (IMC-C225), whereas the parent cells were not. Although the level of **EGFR** expression is of prognostic significance in many tumor models, the response of cells to anti-**EGFR** treatment alone, or **combinations** of this treatment with radiation or chemotherapy, depends upon many factors that are not necessarily related to the inherent **EGFR** expression of the tumor cells. However, the studies reported herein, demonstrate that when LS174T cells were transduced to show increased **EGFR** expression, they became responsive to the radiosensitizing properties of anti-**EGFR** treatments.

L14 ANSWER 11 OF 15 EMBASE

2003257887 EMBASE Gene products involved in metastasis of bladder cancer.
Davies B.R.. Dr. B.R. Davies, Schl. of Surg. and Reproductive Sci., University of Newcastle, Medical School, Newcastle-Upon-Tyne NE2 4HH, United Kingdom. B.R.Davies@ncl.ac.uk. Histology and Histopathology Vol. 18, No. 3, pp. 969-980 2003.
Refs: 104.
ISSN: 0213-3911. CODEN: HIHIES
Pub. Country: Spain. Language: English. Summary Language: English.
Entered STN: 20030717. Last Updated on STN: 20030717

AB Metastasis is usually responsible for mortality in patients suffering from muscle invasive bladder cancer. Whilst expression of a great number of genes and their protein products have been associated with metastasis and/or poor prognosis in bladder cancer, evidence that they actively drive the metastatic process, and hence make potentially good therapeutic targets, is often lacking. This is due to the limited number and application of effective animal models which reflect the pathogenesis of the human disease. In this review I will discuss the processes involved in metastasis, consider the established animal models of bladder cancer progression and metastasis, and review the evidence for a role of various gene products in this process. Consideration of clinical studies in conjunction with evidence from experimental animal models reveals that the tyrosine kinase receptor **erbB1/EGFR**, the calcium binding protein S100A4 and the the cell cycle arrest/apoptosis-inducing p53 protein are amongst the most promising targets for therapy against metastatic disease in patients with bladder cancer.

L14 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 4

2003134501. PubMed ID: 12648471. ErbB-targeted therapeutic approaches in human cancer. Arteaga Carlos L. (Department of Medicine, Vanderbilt University School of Medicine, and Breast Cancer Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, USA.. arlos.artega@vanderbilt.edu) . Experimental cell research, (2003 Mar 10) Vol. 284, No. 1, pp. 122-30. Ref: 100. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB The overexpression and aberrant function of the epidermal growth factor receptor (**EGFR**, **erbB1**, HER1) and its ligands and coreceptors in a wide spectrum of epithelial cancers have provided a rationale for targeting this signaling network with novel treatment approaches. Several antireceptor therapeutic strategies have been pursued, but two stand ahead in their clinical development. One approach has been the generation of small molecules that compete with adenosine triphosphate (ATP) for binding to the receptor's kinase pocket, thus blocking receptor activation and the transduction of postreceptor signals.

The second approach utilizes humanized monoclonal **antibodies** generated against the receptor's ligand-binding extracellular domain. These **antibodies** block binding of receptor-activating ligands and, in some cases, can induce receptor endocytosis and downregulation. Clinical studies already suggest that both of these approaches, either alone or in **combination** with standard anticancer therapies, are well tolerated and can induce clinical responses and tumor stabilization in a variety of common carcinomas.

L14 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2003:143026 Document No. 139:209971 **Combination** of epidermal growth factor receptor targeted therapy with radiation therapy for malignant gliomas. Krishnan, Sunil; Rao, Ravi D.; James, C. David; Sarkaria, Jann N. (Department of Oncology, Mayo Clinic and Foundation, Rochester, MN, USA). Frontiers in Bioscience, 8, E1-E13 (English) 2003. CODEN: FRBIF6. ISSN: 1093-4715. URL: http://WWW.bioscience.org/2003/v8/e/895/pdf.pdf Publisher: Frontiers in Bioscience.

AB A review. Glioblastoma multiform (GBM) are extremely aggressive brain tumors characterized by resistance to standard treatment modalities including surgery, radiation therapy and chemotherapy. While radiation therapy is the standard treatment after surgical resection, these tumors invariably recur and are associated with a uniformly dismal prognosis. Cytotoxic chemotherapy has failed to improve on the modest gains conferred by radiation therapy. Our understanding of the mol. events driving glioma-genesis has led to the recognition of frequent alterations in the epidermal growth factor receptor (**EGFR**) pathway, leading to increased aggressiveness and a poorer prognosis. Based on the importance of **EGFR** in the development of malignancy in multiple tumor types, several classes of novel therapeutic agents have been developed that specifically target **EGFR**. This review outlines the relevance of normal and aberrant **EGFR** signaling in the biol. of gliomas, the strategies for inhibiting **EGFR** activity and the rationale for combining **EGFR** inhibitors with radiation therapy in the treatment of GBM.

L14 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 5
2002046609. PubMed ID: 11751413. Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/neu (erbB2)-overexpressing breast cancer cells in vitro and in vivo. Moulder S L; Yakes F M; Muthuswamy S K; Bianco R; Simpson J F; Arteaga C L. (Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6307, USA.) Cancer research, (2001 Dec 15) Vol. 61, No. 24, pp. 8887-95. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Aberrrant signaling by the epidermal growth factor receptor [**EGFR** (HER1, **erbB1**)] and/or HER2/neu tyrosine kinases is present in a cohort of breast carcinomas. Because HER2 is constitutively phosphorylated in some breast tumors, we speculated that, in these cancers, transmodulation of HER2 may occur via **EGFR** signaling. To test this possibility, we examined the effect of **EGFR** -specific kinase inhibitors against the HER2-overexpressing human breast tumor lines BT-474, SKBR-3, MDA-361, and MDA-453. ZD1839 (Iressa) is an ATP-mimetic that inhibits the purified **EGFR** and HER2 kinases in vitro with an IC(50) of 0.033 and >3.7 microM, respectively. The specificity of ZD1839 against **EGFR** was confirmed in Rat1 fibroblasts transfected with **EGFR** or HER2 chimeric receptors activated by synthetic ligands without the interference of endogenous receptors. Treatment of all breast cancer cell lines (except MDA-453) with 1 microM ZD1839 almost completely eliminated HER2 phosphorylation. In contrast, the incorporation of [gamma-(32)P]ATP in vitro onto HER2 receptors isolated from BT-474 cells was unaffected by 1 microM ZD1839. **EGFR** is expressed by BT-474, SKBR-3, and MDA-361 but not by MDA-453 cells, suggesting that ZD1839-mediated inhibition of the **EGFR** kinase explained the inhibition of HER2 phosphorylation in vivo. In SKBR-3 cells, ZD1839 exhibited a greater growth-inhibitory effect than Herceptin, a monoclonal **antibody** against the HER2

ectodomain. In both SKBR-3 and BT-474 cells, treatment with ZD1839 plus Herceptin induced a greater apoptotic effect than either inhibitor alone. Finally, ZD1839 completely prevented growth of BT-474 xenografts established in nude mice and enhanced the antitumor effect of Herceptin. These data imply that **EGFR** tyrosine kinase inhibitors will be effective against HER2-overexpressing breast tumor cells that also express **EGFR** and support their use in **combination** with HER2 **antibodies**, such as Herceptin, against mammary carcinomas with high levels of the HER2 proto-oncogene.

L14 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 6
2001098135. PubMed ID: 11156523. Molecular mechanisms underlying ErbB2/HER2 action in breast cancer. Harari D; Yarden Y. (Department of Biological Regulation, the Weizmann Institute of Science, Rehovot, Israel.) Oncogene, (2000 Dec 11) Vol. 19, No. 53, pp. 6102-14. Ref: 198. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Overexpression of ErbB2, a receptor-like tyrosine kinase, is shared by several types of human carcinomas. In breast tumors the extent of overexpression has a prognostic value, thus identifying the oncoprotein as a target for therapeutic strategies. Already, **antibodies** to ErbB2 are used in **combination** with chemotherapy in the treatment of metastasizing breast cancer. The mechanisms underlying the oncogenic action of ErbB2 involve a complex network in which ErbB2 acts as a ligand-less signaling subunit of three other receptors that directly bind a large repertoire of stroma-derived growth factors. The major partners of ErbB2 in carcinomas are **ErbB1** (also called **EGFR**) and ErbB3, a kinase-defective receptor whose potent mitogenic action is activated in the context of heterodimeric complexes. Why ErbB2-containing heterodimers are relatively oncopotent is a function of a number of processes. Apparently, these heterodimers evade normal inactivation processes, by decreasing the rate of ligand dissociation, internalizing relatively slowly and avoiding the degradative pathway by returning to the cell surface. On the other hand, the heterodimers strongly recruit survival and mitogenic pathways such as the mitogen-activated protein kinases and the phosphatidylinositol 3-kinase. Hyper-activated signaling through the ErbB-signaling network results in dysregulation of the cell cycle homeostatic machinery, with upregulation of active cyclin-D/CDK complexes. Recent data indicate that cell cycle regulators are also linked to chemoresistance in ErbB2-dependent breast carcinoma. Together with D-type cyclins, it seems that the CDK inhibitor p21waf1 plays an important role in evasion from apoptosis. These recent findings herald a preliminary understanding of the output layer which connects elevated ErbB-signaling to oncogenesis and chemoresistance.

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L15 1 L12 AND MAB425

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L15 ANSWER 1 OF 1 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2006500693 EMBASE Peptabody-EGF: A novel apoptosis inducer targeting **ErbB1** receptor overexpressing cancer cells. Fattah O.M.; Cloutier S.M.; Kundig C.; Felber L.M.; Gygi C.M.; Jichlinski P.; Leisinger H.-J.; Gauthier E.R.; Mach J.P.; Deperthes D.. D. Deperthes, Urology Research Unit/Med Discovery S.A., Biopole, Ch. Croisettes 22, CH-1066 Epalinges, Switzerland. david.deperthes@med-discovery.com. International Journal of Cancer Vol. 119, No. 10, pp. 2455-2463 15 Nov 2006.
Refs: 29.
ISSN: 0020-7136. E-ISSN: 1097-0215. CODEN: IJCNAW
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20061027. Last Updated on STN: 20061027

AB The epidermal growth factor receptor (**EGFR**) plays a central role

in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of **EGFR** represents a very promising challenge in oncology, and **antibodies** raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such **antibodies**, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or combinations thereof. We report here the development of an alternative high affinity molecule that is directed against **EGFR**. Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of **EGFR**. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing **EGFR**. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal **EGFR antibody** Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on **EGFR** overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-**EGFR** therapy. .COPYRGT. 2006 Wiley-Liss, Inc.

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=> s l11 and "MAb 425"
L16           7 L11 AND "MAB 425"

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PROCESSING COMPLETED FOR L16
L17           3 DUP REMOVE L16 (4 DUPLICATES REMOVED)

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L17  ANSWER 1 OF 3     MEDLINE on STN                    DUPLICATE 1
2006581555.    PubMed ID: 16858684.   Peptabody-EGF: a novel apoptosis inducer
     targeting ErbB1 receptor overexpressing cancer cells. Fattah
     Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi
     Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R;
     Mach Jean Pierre; Deperthes David. (Department of Urology, Urology
     Research Unit, CHUV, Epalinges, Switzerland. ) International journal of
     cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10,
     pp. 2455-63.  Journal code: 0042124. ISSN: 0020-7136. Pub. country: United
     States. Language: English.
AB   The epidermal growth factor receptor (EGFR) plays a central role in cell
     life by controlling processes such as growth or proliferation.  This
     receptor is commonly overexpressed in a number of epithelial malignancies
     and its upregulation is often associated with an aggressive phenotype of
     the tumor.  Thus, targeting of EGFR represents a very promising challenge
     in oncology, and antibodies raised against this receptor have
     been investigated as potential antitumor agents.  Various putative
     mechanisms of action were proposed for such antibodies,
     including decreased proliferation, induction of apoptosis, stimulation of
     the immunological response against targeted cancer cells or combinations
     thereof.  We report here the development of an alternative high affinity
     molecule that is directed against EGFR.  Production of this pentameric
     protein, named peptabody-EGF, includes expression in a bacterial
     expression system and subsequent refolding and multimerization of
     peptabody monomers.  The protein complex contains 5 human EGF ligand
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domains, which confer specific binding towards the extracellular portion of EGFR. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing EGFR. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal EGFR **antibody Mab-425.** Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on EGFR overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-EGFR therapy.

L17 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB **antibodies** and their use in tumor therapy. Kreysch, Hans-Georg (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.

AB The invention relates to novel bispecific **antibodies** and their use in tumor therapy. The novel **antibodies** have the ability to bind to ErbB receptors, preferably **ErbB1** receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these **antibodies** are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal **antibodies MAb 425** and chimeric MAb 225 was presented.

L17 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. Kreysch, Hans-Georg; Schmidt, Juergen (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal **antibodies** (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred **antibodies** according to this invention are **MAb 425** and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for **antibody**-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two **antibodies** with specificity for different epitopes of the human

EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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L18 16660 (KREYSCH H?/AU OR SCHMIDT J?/AU)

=> s l18 and anti-EGFR1
L19 0 L18 AND ANTI-EGFR1

=> s l18 and ErbB1 antibody
L20 0 L18 AND ERBB1 ANTIBODY

=> s l18 and antibod?
L21 586 L18 AND ANTIBOD?

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L22 3 L21 AND EGFR

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L23 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. **Kreysch, Hans-Georg; Schmidt, Juergen** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

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L23 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2003:502686 Document No.: PREV200300498451. The humanized monoclonal anti-**EGFR antibody** EMD72000 potently inhibits the growth of **EGFR**-expressing human tumor xenografts insensitive to chemotherapeutic drugs. Burger, Angelika M. [Reprint Author]; Heiss, Nina S.; **Kreysch, Hans-Georg**; Schandelmaier, Kathrin; Wirth, Gregory; Fiebig, Heinz H.; Grell, Matthias. Oncotest, Freiburg, Germany. Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 1139. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer

Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X. Language: English.

L23 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2002:539555 Document No. 137:108304 Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting **antibodies** and angiogenesis inhibitors for treating cancer and metastasis. Goodman, Simon; **Kreysch, Hans-Georg** (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2002055106 A2 20020718, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP15241 20011221. PRIORITY: EP 2001-100507 20010109.
AB The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of receptor tyrosine kinase antagonists/inhibitors, especially ErbB receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or radiation therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone.

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L25 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB **antibodies** and their use in tumor therapy. **Kreysch, Hans-Georg** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.
AB The invention relates to novel bispecific **antibodies** and their use in tumor therapy. The novel **antibodies** have the ability to bind to ErbB receptors, preferably **ErbB1** receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these **antibodies** are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal **antibodies** MAb 425 and chimeric MAb 225 was presented.

L25 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. **Kreysch, Hans-Georg; Schmidt, Juergen** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal **antibodies** (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred **antibodies** according to this invention are MAb 425 and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for **antibody**-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two **antibodies** with specificity for different epitopes of the human EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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L27 ANSWER 1 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2007060458 EMBASE Four Cases of Sirolimus-Associated Interstitial Pneumonitis: Identification of Risk Factors. Morath C.; Schwenger V.; Ksoll-Rudek D.; Sommerer C.; Beimler J.; **Schmidt J.**; Zeier M..
C. Morath, Department of Nephrology, University of Heidelberg, Heidelberg, Germany. christian_morath@med.uni-heidelberg.de. Transplantation Proceedings Vol. 39, No. 1, pp. 99-102 2007.
Refs: 21.
ISSN: 0041-1345. CODEN: TRPPA8
S 0041-1345(06)01482-5. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070319. Last Updated on STN: 20070319

AB Sirolimus-associated interstitial pneumonitis is a severe side effect of sirolimus therapy; fatal outcomes have been described. We report 4 patients with sirolimus-associated interstitial pneumonitis and review the literature for risk factors for the development of disease. Until June 2005, 48 patients received either de novo sirolimus treatment (n = 7) or were switched from a calcineurin inhibitor-containing regimen to a sirolimus-based protocol for various indications (n = 41). Compared with the 44 patients on sirolimus therapy with no evidence of a disorder, the 4 patients (8.3%) who developed suspected sirolimus-associated interstitial pneumonitis showed no difference in gender, immunosuppressive therapy, days posttransplantation, comorbidity, or preexistent lung disease. Several points, however, are of interest. None of the de novo-treated patients except 4 patients (9.8%) with late administration of sirolimus developed interstitial pneumonitis. The 4 patients with interstitial

pneumonitis tended to be older (58.7 ± 5.5 vs 46.9 ± 1.7 years) and received higher sirolimus doses (3.5 ± 0.5 vs 1.4 ± 0.2 mg/d) with greater trough levels (15.4 ± 2.9 vs 8.0 ± 1.2 μg/L) at the onset of symptoms. Most notably, all patients with interstitial pneumonitis had a loading dose at the start of therapy, and an increase in sirolimus dose (or trough level) within 3 weeks prior to the onset of symptoms. Additional potential risk factors identified from the literature include allograft dysfunction, hypervolemia, and male gender. With careful monitoring (or even exclusion from therapy) of patients at risk for the development of disease, we have had no case of sirolimus-associated interstitial pneumonitis since September 2004.

L27 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1070279 Document No. 145:410678 Methods for treating infectious disease exacerbated asthma using CpG oligonucleotides. Krieg, Arthur M.; De Sanctis, George Tilo; Underwood, Stephen Leslie; Jupp, Raymond Anthony; **Schmidt, John A.** (Coley Pharmaceutical Group, Inc., USA; Sanofi-Aventis U.S.P. LLC). U.S. Pat. Appl. Publ. US 2006229271 A1 20061012, 60pp. (English). CODEN: USXXCO. APPLICATION: US 2006-401093 20060410. PRIORITY: US 2005-669548P 20050408.

AB It has been discovered herein that CpG oligonucleotides (CpG ODN) are particularly effective in combating infections, and particularly upper respiratory tract virus, that are a cause of asthma exacerbations. In some aspects of the invention C-class CpG ODN are particularly effective for carrying out the methods. As shown in the Examples below, C-class CpG ODN induced a panel of IFN-associated genes in the mouse, including those for antiviral proteins, and protected against airway inflammation exacerbated by combined antigen and virus exposures.

L27 ANSWER 3 OF 14 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:1051354 The Genuine Article (R) Number: 096WU. PEG-hirudin/iloprost coating of small diameter ePTFE grafts effectively prevents pseudointima and intimal hyperplasia development. Heise M (Reprint); Schmidmaier G; Husmann I; Heidenhain C; **Schmidt J**; Neuhaus P; Settmacher U. Univ Med, Charite, Dept Gen Surg, Augustenburger Pl 1, D-13353 Berlin, Germany (Reprint); Univ Med, Charite, Dept Gen Surg, D-13353 Berlin, Germany; Charite, Ctr Musculoskeletal Surg, D-13353 Berlin, Germany. michael.heise@charite.de. EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY (OCT 2006) Vol. 32, No. 4, pp. 418-424. ISSN: 1078-5884. Publisher: W B SAUNDERS CO LTD, 32 JAMESTOWN RD, LONDON NW1 7BY, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives. Small diameter PTFE grafts are prone to thrombosis and intimal hyperplasia development. Heparin graft coating has beneficial effects but also potential drawbacks. The purpose of this study was to evaluate the experimental efficacy of PEG-hirudin/iloprost coated small caliber PTFE grafts.

Methods. Thirty-six femoro-popliteal ePTFE grafts (expanded polytetrafluoroethylene, diameter 4 mm) were inserted into 18 pigs. Grafts were randomised individually for each leg and grouped for 3 groups. Group 1 consisted of native ePTFE grafts, group II were grafts coated with a polylactide polymer (PLA) without drugs and group III grafts were coated with PLA containing a polyethylene glycol (PEG)-hirudin/iloprost **combination.** The follow-up period was 6 weeks. Patency rates were calculated and development of pseudointima inside the grafts was noted. Thickness of intimal hyperplasia at the distal anastomoses was measured using light microscopy.

Results. Patency rates for group I were 6/9 (67%), for group II 9/10 (90%) and 12/12 (100%) for group III. In groups I and II there was a significant reduction of blood flow proximal to the graft at graft harvest, to 29 +/- 12 and 28 +/- 20 ml/min respectively (both $p < 0.01$ versus preoperative value), whilst in group III blood flow, 99 +/- 21 ml/min, remained at the preoperative level. Subtotal stenosis due to

development of pseudointima was noted in each of the native and PLA coated grafts but not in group III grafts. Intimal hyperplasia at the distal anastomosis was lowest in group III.

Conclusions. The PEG-hirudin/iloprost coating of ePTFE prostheses effectively reduced pseudointima and intimal hyperplasia development and led to superior graft patency.

L27 ANSWER 4 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006381737 EMBASE Phase II evaluation of docetaxel plus exisulind in patients with androgen independent prostate carcinoma. Sinibaldi V.J.; Elza-Brown K.; **Schmidt J.**; Eisenberger M.A.; Rosenbaum E.; Denmeade S.R.; Pili R.; Walczak J.; Baker S.D.; Zahurak M.; Carducci M.A.. Dr. V.J. Sinibaldi, Johns Hopkins Medical Institutions, 550 North Broadway, Baltimore, MD 21205, United States. sinibvi@jhmi.edu. American Journal of Clinical Oncology: Cancer Clinical Trials Vol. 29, No. 4, pp. 395-398 2006.

Refs: 12.

ISSN: 0277-3732. E-ISSN: 1537-453X. CODEN: AJCODI

00000421200608000000013. Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 20060823. Last Updated on STN: 20060823

AB OBJECTIVES: In this phase II study, the **combination** of docetaxel and exisulind (a GMP phosphodiesterase inhibitor) was given to patients with metastatic androgen independent prostate cancer (AIPC) to establish efficacy, assess toxicity, and determine pharmacokinetics of docetaxel administered alone and in **combination** with exisulind. METHODS: Fourteen patients with metastatic AIPC were registered to receive weekly docetaxel for 4 weeks, followed by 2 weeks of rest; repeated up to a maximum of 6 cycles. Exisulind 250 mg was given orally twice a day starting on day 8 of the study and taken continuously. RESULTS: All patients were evaluable for toxicity, response and survival. Grade 3 reversible toxicities included: fatigue, nausea, diarrhea, abdominal pain, rash, syncope, pulmonary edema, deep vein thrombosis, congestive heart failure, and elevations in transaminases, requiring therapy delays and/or dose reductions, or removal from therapy. Only 3 out of 14 patients (21.4%) had a 50% decline in prostate specific antigen (PSA) level that lasted ≥4 weeks; 1 out of 14 patients (7%) had a lymph node response. Median survival was 17.28 months. Docetaxel pharmacokinetics for 11 patients demonstrated mean ± SD clearance values that were similar during week 1 and week 3 when exisulind had been added. CONCLUSIONS: Overall, our trial indicated that the toxicity profile and efficacy of this regimen is unlikely to be substantially better than single agent docetaxel.

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2006544211 EMBASE Immunosuppressive standards in simultaneous kidney-pancreas transplantation. Schmied B.M.; Muller S.A.; Mehrabi A.; Welsch Th.; Buchler M.W.; Zeier M.; **Schmidt J.**. Dr. B. Schmied, Chirurgische Klinik, Universitat Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany. bruno.schmied@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 44-50 2006.

Refs: 40.

ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 20061122. Last Updated on STN: 20061122

AB Simultaneous pancreas-kidney transplantation is an established procedure for patients with type I diabetes and end-stage renal disease. Continuous advances in the operation techniques with consequent reduction of perioperative morbidity and mortality and the introduction of modern immunosuppressive agents improved not only patients but also graft survival and significantly decreased rejection episodes of both kidney and

pancreas grafts. Availability of a variety of new immunosuppressants in the clinical routine and increasing experience of the transplant specialists allowed further developments of therapeutic schemes with application of induction and maintenance immunosuppressive protocols. In this article, we summarize the current status of immunosuppressive regimens in simultaneous pancreas and kidney transplantation. .COPYRGT. 2006 Blackwell Munksgaard.

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2006544210 EMBASE The role and value of sirolimus administration in kidney and liver transplantation. Mehrabi A.; Fonouni H.; Kashfi A.; Schmied B.M.; Morath Ch.; Sadeghi M.; Schemmer P.; Encke J.; Sauer P.; Zeier M.; Weitz J.; Buchler M.W.; **Schmidt J.**. Dr. A. Mehrabi, Division of Visceral Transplantation, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany. arianeb_mehrabi@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 30-43 2006.
Refs: 58.
ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061122. Last Updated on STN: 20061122

AB Enormous advancements in visceral transplantation have led to significant improvements in the quality of life of patients. However, despite these developments, the average graft half-life after transplantation has remained almost unchanged and chronic rejection is still considered a major problem. In this regard, more concerns have shifted to factors influencing long-term graft survival, patient survival, and quality of life. To achieve this goal, detrimental effects of immunosuppressive (IS) agents, which have deleterious influence on the quality of life and/or patient survival, should be reduced. In the course of recent years, the transplant community has worked on reducing these side effects by developing new ISs, employing new **combination** regimens, or finding and adjusting optimal dosages and blood level concentrations. Among the IS agents, the antifungal, antitumoral and IS activity of mammalian target of rapamycin (mTOR) inhibitors without nephrotoxicity, have received special attention regarding this new class of IS. Sirolimus (SRL), as the first member of mTOR inhibitors, has been utilized in many clinical trials with respect to its benefit-risk assessment. In our review, the clinical evolution of SRL, as well as the evidence-based clinical benefits of SRL in kidney and liver transplantation (KTx, LTx), are summarized. Various studies of SRL in KTx and LTx have shown that **combination** therapy with SRL will enrich the variety of IS modalities. It also can be regarded as a safe base therapy to which other necessary drugs can be added. In addition to the enhanced acute rejection prophylaxis, and in contrast to the calcineurin inhibitors (CNI) and steroids, this drug solely does not have common side effects such as nephrotoxicity, neurotoxicity, diabetes mellitus and hypertension. Moreover, this agent might diminish vasculopathic processes that mediate chronic allograft nephropathy (CAN). Therefore, by reducing the likelihood of CAN it can decrease the rate of long-term organ failure. One possibly desirable characteristic of SRL is its antiproliferative effect, which could provoke antitumoral or antiatherogenic activity following transplantation. Despite all promising impacts of SRL in organ transplantation, there are some concerns regarding the adverse effects of this drug, for instance dyslipidemia, pneumonitis and wound healing problems. However, the majority of these side effects can be reduced or ceased by careful dose adjustments and correct timing of use. In conclusion, after a decade of both in vivo and in vitro studies on SRL, it can be advocated that SRL is a promising, potent and effective IS agent as it reduces the rate of acute rejection episodes in de novo transplants. It could improve the quality of life, graft and patient survival rate, and achieve excellent outcomes with few adverse effects when wisely used in **combination** with other immunosuppressants. .COPYRGT. 2006

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L27 ANSWER 7 OF 14 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2005:479942 Document No.: PREV200510266527. Cytotoxic activity of cytokine-induced killer cells correlates with expression of SAP and SLAM. Mehrle, Stefan [Reprint Author]; Frank, Susanne; **Schmidt, Jan**; Buchler, Markus W.; Schmidt-Wolf, Ingo G. H.; Marten, Angela. Univ Heidelberg, Dept Surg, D-6900 Heidelberg, Germany. Blood, (NOV 16 2004) Vol. 104, No. 11, Part 2, pp. 55B-56B.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB SAP is a small protein, consisting of a single SH2 domain which is mutant in humans with X-linked lymphoproliferative disease. Patients with XLP are affected by fatal EBV infections and malignant B cell lymphomas. The increased risk for B cell lymphomas is suggested to result from impaired immunosurveillance ofB cell proliferation by T cells. Here, we investigated the role of SLAM/SAP for activation of effector cells with cytotoxic activity (CIK cells), which aregenerated by unspecific stimulation of the T cell receptor and addition of exogenous IL-2 as described previously. The TCR activation on day +1 resulted not only in a

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L6 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
95403469. PubMed ID: 7673253. Heregulin activation of extracellular acidification in mammary carcinoma cells is associated with expression of HER2 and HER3. Chan S D; Antoniucci D M; Fok K S; Alajoki M L; Harkins R N; Thompson S A; Wada H G. (Molecular Devices Corporation, Sunnyvale, California 94089, USA.) The Journal of biological chemistry, (1995 Sep 22) Vol. 270, No. 38, pp. 22608-13. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB HER2, the **erbB**-2/neu proto-oncogene product, is a 185-kDa transmembrane glycoprotein related to the epidermal growth factor receptor. Overexpression of HER2 was reported in several human

adenocarcinomas, including mammary and ovarian carcinomas. A family of glycoproteins, the heregulin/neu differentiation factors, was characterized and implicated as the ligands for HER2. Recently, it has been shown that HER2 alone is not sufficient to reconstitute high affinity heregulin receptors and that HER3 or HER4 may be the required components of the heregulin receptors on mammary carcinoma cells (Sliwkowski, M.X., Schaefer, G., Akita, R.W., Lofgren, J.A., Fitzpatrick, V.D., Nuijens, A., Fendly, B.M., Cerione, R.A., Vandlen, R.L., and Carraway, K.L., III (1994) J. Biol. Chemical 269, 14661-14665; Plowman, G.D., Green, J.M., Culouscou, J.-M., Carlton, G.W., Rothwell, V.M., and Buckley, W. (1993) Nature 366, 473-475). Using the Cytosensor to measure the extracellular acidification rate, we have examined the effects of recombinant human heregulin-alpha on three mammary carcinoma cell lines expressing HER2 (MDA-MB-453, SK-BR-3, and MCF-7), an ovarian carcinoma cell line expressing HER2 (SK-OV-3), and CHO-**K1** and 293-EBNA cells stably transfected with HER2. By reverse transcription polymerase chain reaction and Western blotting, we found that the breast cells also express HER3 and that the ovarian line co-expresses the HER4 message. A dramatic increase in the acidification rate was observed for the mammary carcinoma cells co-expressing high levels of HER2 and HER3. In contrast, the ovarian cells expressing high levels of HER2 and low levels of HER4 or CHO-**K1** and 293-EBNA cells expressing HER2 alone were not responsive to heregulin. When these same transfected cells were exposed to monoclonal anti-HER2 **antibody** followed by anti-IgG to cause aggregation of the HER2 molecules, an increase in the acidification rate was observed, indicating coupling of transfected HER2 to the signal transduction pathway. Transfection of HER2 into MCF-7 cells, on the other hand, gave 4-fold enhanced acidification responses. These data, together with the previously reported high affinity heregulin binding and activation of tyrosine phosphorylation in HER2 and HER3 co-transfected cells support the role of HER2 and HER3 as components of the heregulin receptor in breast cells.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

1995:254144 Document No. 122:47384 Keratinocyte growth factor receptor ligands induce transforming growth factor α expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz, Andrzej A.; Cheng, Christina; Denning, Mitchell F.; Dempsey, Peter J.; Coffey, Robert J., Jr.; Yuspa, Stuart H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, MD, 20892, USA). Cell Growth & Differentiation, 5(12), 1283-92 (English) 1994. CODEN: CGDIE7. ISSN: 1044-9523. Publisher: American Association for Cancer Research.

AB EGF receptor (EGFR) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor α (TGFα) and EGF elicit distinctive changes in keratin expression: Ca2+-mediated induction of the differentiation-specific keratins **K1** and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., 1993). We have evaluated several addnl. growth factors to determine the specificity of this response for EGFR ligands. TGFα, keratinocyte growth factor (KGF), and acidic FGF (aFGF), but not basic FGF (bFGF) or IGF-I, block Ca2+-mediated expression of **K1** while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGFα/EGFR pathway is an intermediary in signaling through the KGFR. TGFα mRNA was increased in cells treated with KGF, aFGF, or TGFα but not bFGF or IGF-I. Similar changes were detected at the protein level; TGFα in conditioned medium (CM) from control, KGF-, TGFα-, and aFGF-treated cultures was 54, 365, 146, and 120 pg/mL, resp. KGF and TGFα also increased expression of cell-associated TGFα measured in keratinocyte lysates. KGF increased TGFα secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with

neutralizing **antibodies** or both TGFα and KGF, but not KGF **antibody** alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGFα. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGFα resulted in EGFR autophosphorylation. Furthermore, after .apprx.24 h, KGF as well as TGFα induced EGFR down-regulation based on Western blot anal. and 125I-EGF binding. Induction of TGFα in KGF-treated keratinocytes, coupled to activation and down-modulation of the EGFR, suggests that TGFα may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L6 ANSWER 3 OF 3 MEDLINE on STN
92290622. PubMed ID: 1351045. Frequent expression of the tumor antigen CAK1 in squamous-cell carcinomas. Chang K; Pastan I; Willingham M C. (Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) International journal of cancer. Journal international du cancer, (1992 Jun 19) Vol. 51, No. 4, pp. 548-54. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB **K1** is a murine monoclonal **antibody** (MAb) derived from a hybridoma generated by the fusion of splenocytes of BALB/c mice immunized with a human ovarian tumor cell line, OVCAR-3. This **antibody** reacts strongly with epithelial ovarian tumors and mesotheliomas. The antigen recognized by MAb **K1**, designated CAK1, has recently been characterized as a 40-kDa protein probably anchored to the cell surface by glycosyl-phosphatidylinositol. Using immunoperoxidase histochemical methods, we examined 37 squamous-cell carcinoma (SqCC) samples from cervix, lung, esophagus and other origins, and 12 normal squamous epithelia of the cervix and esophagus for their reactivity with MAb **K1**. Of the SqCC specimens, 81% showed **K1** reactivity with variable intensity, but none of 12 normal tissue samples of squamous epithelia did so. Two patterns of CAK1 expression in tumor samples were found, i.e., a heterogeneous pattern with strong intensity, and a homogeneous pattern with weak intensity. Three carcinomas in situ of the larynx, vulva and esophagus were moderately positive with **K1**, suggesting that CAK1 antigen may occur in the early stage of carcinogenesis of SqCC. The expression of CAK1 was also compared with expression of CA125, HER-2/neu, p53 and P-glycoprotein, and MAb **K1** was found to react most consistently with SqCC. Since **K1** reacts with a majority of cervical and esophageal carcinomas but has no detectable reactivity in normal epithelia of the cervix uteri and esophagus, MAb **K1** could be of value as a reagent to help distinguish between normal and neoplastic cells on sections as well as in cytological samples.

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L9 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2006718900. PubMed ID: 16886908. Selection and characterization of an internalizing epidermal-growth-factor-receptor **antibody.** Zhao Xiaorong; Dai Wentao; Cao Limin; Zhu Huifen; Yu Yihan; Ye Qing; Wang Min; Dai Wei; Lei Ping; Shen Guanxin. (Laboratory of Molecular and Immuno-Pharmacology, Department of Immunology Tongji Medical College,

Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China.) Biotechnology and applied biochemistry, (2007 Jan) Vol. 46, No. Pt 1, pp. 27-33. Journal code: 8609465. E-ISSN: 1470-8744. Pub. country: England: United Kingdom. Language: English.

AB **Antibody**-therapeutic agent conjugates to be delivered directly into the cytosol of tumour cells is required for many target-based therapeutic strategies. For this work, a large non-immune phage-display library was used to select internalizing scFv (single chain variable fragment) directed against **EGFR** (epidermal growth factor receptor), a tyrosine kinase receptor that is overexpressed in a wide range of tumour cells. The CHO-**EGFR**-GFP1 (where CHO is Chinese-hamster ovary) cell line, a transfected cell line expressing **EGFR**-GFP (green fluorescent protein) fusion protein on membranes, and the untransfected cell line CHO-**K1** were used as **EGFR** -positive cells and -negative cells respectively in the subtractive selection procedure. A novel human anti-**EGFR** scFv (F4-scFv) was isolated. F4-scFv bound native **EGFR**-bearing cell lines and could be internalized, but did not bind **EGFR**-negative cell lines. The K(D) value of F4-scFv was 472 nM as determined on A431 cells. F4-scFv could be used to target therapeutic agents into tumour cells and was expected to be non-immunogenic in humans. Use of a transfected cell line expressing GFP-tagged receptors allows selection and characterization of **antibodies** to native receptors without the need for protein expression and purification, significantly speeding up the generation of targeting **antibodies.**

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2006:297056 Document No.: PREV200600297498. Directed evolution of the epidermal growth factor receptor extracellular domain for expression in yeast. Kim, Yong-Sung; Bhandari, Rashna; Cochran, Jennifer R.; Kuriyan, John; Wittrup, K. Dane [Reprint Author]. MIT, Div Biol Engn, 400 Main St Bldg 66-552, Cambridge, MA 02139 USA. wittrup@mit.edu. Proteins Structure Function and Bioinformatics, (MAR 1 2006) Vol. 62, No. 4, pp. 1026-1035. CODEN: PSFGEY. ISSN: 0887-3585. Language: English.

AB The extracellular domain of epidermal growth factor receptor (**EGFR** -ECD) has been engineered through directed evolution and yeast surface display using conformationally-specific monoclonal **antibodies** (mAbs) as screening probes for proper folding and functional expression in Saccharomyces cerevisiae. An **EGFR** mutant with four amino acid changes exhibited binding to the conformationally-specific mAbs and human epidermal growth factor, and showed increased soluble secretion efficiency compared with wild-type **EGFR.** Full-length **EGFR** containing the mutant **EGFR**-ECD was functional, as assayed by EGF-dependent autophosphorylation and intracellular MAPK signaling in mammalian cells, and was expressed and localized at the plasma membrane in yeast. This approach should enable engineering of other complex mammalian receptor glycoproteins in yeast for genetic, structural, and biophysical studies.

L9 ANSWER 3 OF 7 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2006251624 EMBASE The efficacy of alginate encapsulated CHO-**K1** single chain-TRAIL producer cells in the treatment of brain tumors. Kuijlen J.M.A.; de Haan B.J.; Helfrich W.; de Boer J.-F.; Samplonius D.; Mooij J.J.A.; de Vos P.. J.M.A. Kuijlen, Department of Neurosurgery, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, Netherlands. j.m.a.kuijlen@nchir.umcg.nl. Journal of Neuro-Oncology Vol. 78, No. 1, pp. 31-39 2006.
Refs: 23.
ISSN: 0167-594X. E-ISSN: 1573-7373. CODEN: JNODD2
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060615. Last Updated on STN: 20060615

AB Object: Patients with astrocytic tumors in the central nervous system (CNS) have low survival rates despite surgery and radiotherapy. Innovative therapies and strategies must be developed to prolong survival

of these patients. The alginate microencapsulation method, used to continuously release a certain cytotoxic agent in the vicinity of the tumor, is such a novel therapeutic strategy. The biological functionality of the apoptosis inducing scFv425:sTRAIL protein, which was released through the microencapsulation method, was studied in vitro. Analysis of the intracerebral biocompatibility of alginate capsules was performed by implantation of empty alginate capsules in the brain of mice. Method: Chinese Hamster Ovary cells (CHO-**K1**) were recombinantly engineered to produce the single chain anti-**EGFR**-sTRAIL protein (scFv425:sTRAIL). The CHO-**K1** producer cells were encapsulated in an alginate capsule with a semi-permeable membrane through which the scFv425:sTRAIL protein could be released. Results: In vitro studies show maintained biological functionality of the released scFv425:sTRAIL protein. There was no immunological tissue response detectable after intracerebral implantation of the alginate capsules in mice brains. Conclusion: Biological functionality of the produced scFv425:sTRAIL protein is maintained and intracerebral biocompatibility of the capsules is warranted. Alginate encapsulation of CHO-**K1** - scFv425:sTRAIL - producer cells and subsequently their intracerebral implantation is technically feasible. This study justifies further in vivo experiments. .COPYRGT. Springer Science+Business Media, Inc. 2006.

L9 ANSWER 4 OF 7 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2001:331622 The Genuine Article (R) Number: 422QK. Proliferation and differentiation of the keratinocytes in hyperplastic epidermis overlying dermatofibroma - Immunohistochemical characterization.. Han K H; Huh C H; Cho K H (Reprint). Seoul Natl Univ Hosp, Dept Dermatol, Chongno Gu, 28 Yongon Dong, Seoul 110744, South Korea (Reprint); Seoul Natl Univ Hosp, Clin Res Inst, Lab Cutaneous Aging Res, Chongno Gu, Seoul 110744, South Korea; Seoul Natl Univ, Coll Med, Dept Dermatol, Seoul 110744, South Korea . AMERICAN JOURNAL OF DERMATOPATHOLOGY (APR 2001) Vol. 23, No. 2, pp. 90-98. ISSN: 0193-1091. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Epidermal changes overlying dermatofibromas (DFs) have been described as ranging from psoriasiform simple hyperplasia to basaloid hyperplasia sometimes morphologically indistinguishable from superficial basal cell carcinoma (BCC). To characterize epidelmal hyperplasia overlying DFs and to determine its association with the disease process, we examined 30 cases of DF showing hyperplastic epidermis. We used nine immunohistochemical markers associated with keratinocyte proliferation or differentiation. In DFs, the dermal metallothionein (MT) expression and immunophenotypic changes with regard to epidermal differentiation varied depending on the stage of lesional evolution of the DFs. Immunostaining for epidermal growth factor receptor (**EGFR**), MT, and keratin 6 (K6) increased in simple hyperplastic epidermis (SHE) overlying DFs (n = 11), whereas it gradually diminished in basaloid hyperplastic epidermis (BHE) overlying DFs (n = 19). In SHE, there was a significant increase in K14 expression. Among 19 BHE: cases, 12 showed premature expression of involucrin and delayed appearance of **K1** along with aberrant expression of K14. Conversely, the remaining 7 BHE cases showed a pattern of involucrin and **K1** similar to that of normal skin coinciding with decreased or absent dermal M7 expression. Loricrin and filaggrin expression in all DFs was the same as that of normal skin. Based on the sparse positivity of Ki-67 in the hyperplastic epidermis overlying DFs, we found that the biologic ability of BHE and SHE was not apparent in the hyperproliferative state observed in psoriasis and BCC. Thee results suggest that the dermal fibrohistiocytic process may trigger the induction of SHE overlying DFs by an unknown mechanism and then mediate both the abnormal keratinocyte differentiation and the transformation of SHE to BHE through the evolution of the dermal lesions.

L9 ANSWER 5 OF 7 MEDLINE on STN

97384952. PubMed ID: 9242447. Targeted disruption of the epidermal growth

factor receptor impairs growth of squamous papillomas expressing the v-ras(Ha) oncogene but does not block in vitro keratinocyte responses to oncogenic ras. Dlugosz A A; Hansen L; Cheng C; Alexander N; Denning M F; Threadgill D W; Magnuson T; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892, USA.) Cancer research, (1997 Aug 1) Vol. 57, No. 15, pp. 3180-8. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB We have assessed the role of epidermal growth factor receptor (**EGFR**) signaling in biological responses to the v-ras(Ha) oncogene using primary keratinocytes from **Egfr** -/- mice and wild-type littermates. On the basis of several criteria, **Egfr** -/- keratinocytes were unresponsive to either acute or chronic exposure to several **EGFR** ligands but were stimulated to proliferate in response to several other mitogens. Although conditioned medium from primary keratinocytes transduced with v-ras(Ha) retrovirus (v-ras(Ha) keratinocytes) was a potent mitogen for wild-type but not **Egfr** -/- keratinocytes, v-ras(Ha) transduction of primary keratinocytes of either genotype resulted in a strong mitogenic response, arguing against an obligatory role for **EGFR** activation in v-ras(Ha)-mediated stimulation of keratinocyte proliferation. Infection with high-titer v-ras(Ha) retrovirus altered the keratin expression pattern in keratinocytes of both genotypes, suppressing differentiation-specific keratins **K1** and K10 while activating aberrant expression of K8 and K18. In wild-type but not **Egfr** -/- cultures, **K1** and K10 were also suppressed following infection at lower retroviral titers, presumably as a result of paracrine **EGFR** activation on uninfected cells present in these cultures. Squamous papillomas produced by grafting **Egfr** -/- v-ras(Ha) keratinocytes onto nude mice were only 21% of the size of wild-type v-ras(Ha) tumors, and a striking redistribution of S-phase cells was detected by immunostaining for bromodeoxyuridine. In **Egfr** -/- v-ras(Ha) papillomas, the fraction of total labeled nuclei detected in suprabasal layers was increased from 19 to 39%. In contrast, the basal layer labeling index of **Egfr** -/- papillomas was reduced to 34%, compared to 43% in wild-type tumors. Our results indicate that, although autocrine **EGFR** signaling is not required for keratinocyte responses to oncogenic ras in culture or benign tumor formation in nude mouse grafts, disruption of this pathway impairs growth of v-ras(Ha) papillomas by a mechanism that may involve alterations in keratinocyte cell cycle progression and/or migration in vivo.

L9 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 3

95210161. PubMed ID: 7535082. Keratinocyte growth factor receptor ligands induce transforming growth factor alpha expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz A A; Cheng C; Denning M F; Dempsey P J; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892.) Cell growth & differentiation : the molecular biology journal of the American Association for Cancer Research, (1994 Dec) Vol. 5, No. 12, pp. 1283-92. Journal code: 9100024. ISSN: 1044-9523. Pub. country: United States. Language: English.

AB Epidermal growth factor receptor (**EGFR**) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor alpha (TGF alpha) and EGF elicit distinctive changes in keratin expression: Ca(2+)-mediated induction of the differentiation-specific keratins **K1** and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., Cell Growth, & Differ., 4: 317-327, 1993). We have evaluated several additional growth factors to determine the specificity of this response for **EGFR** ligands. TGF alpha, keratinocyte growth factor (KGF), and acidic fibroblast growth factor (aFGF), but not basic fibroblast growth factor (bFGF) or insulin-like

growth factor type I, block Ca(2+)-mediated expression of **K1** while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGF alpha/ **EGFR** pathway is an intermediary in signaling through the KGFR. TGF alpha mRNA was increased in cells treated with KGF, aFGF, or TGF alpha but not bFGF or insulin-like growth factor type I. Similar changes were detected at the protein level; TGF alpha in conditioned medium (CM) from control, KGF-, TGF alpha-, and aFGF-treated cultures was 54 (+/- 8, SEM), 365 (+/- 50), 146 (+/- 20), and 120 (+/- 50) pg/ml, respectively. KGF and TGF alpha also increased expression of cell-associated TGF alpha measured in keratinocyte lysates. KGF increased TGF alpha secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with neutralizing **antibodies** to both TGF alpha and KGF, but not KGF **antibody** alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGF alpha. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGF alpha resulted in **EGFR** autophosphorylation. Furthermore, after approximately 24 h, KGF as well as TGF alpha induced **EGFR** down-regulation based on Western blot analysis and 125I-EGF binding. Induction of TGF alpha in KGF-treated keratinocytes, coupled to activation and down-modulation of the **EGFR**, suggests that TGF alpha may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L9 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
1993:6287 Document No.: PREV199395006287. Relationships between Ki-67 labelling index, amplification of the epidermal growth factor receptor gene, and prognosis in human glioblastomas. Torp, S. H. [Reprint author]; Helseth, E.; Dalen, A.; Unsgaard, G.. Inst. Cancer Res., Med. Technical Cancer, N-7005 Trondheim, Norway. Acta Neurochirurgica, (1992) Vol. 117, No. 3-4, pp. 182-186.
CODEN: ACNUA5. ISSN: 0001-6268. Language: English.

AB The aim of this study was to determine possible relationships between Ki-67 labelling index (Ki-67 LI), amplification of the epidermal growth factor receptor (**EGFR**) gene, and prognosis in human glioblastomas. Ki-67 LI was determined on cryosections of biopsy specimens of 20 human glioblastomas with a mouse antihuman Ki-67 monoclonal **antibody.** Amplification of the **EGFR** gene was determined by slot blot and Southern blot analyses of DNA extracted from the tumour biopsies. The Ki-67 LI was higher in the glioblastoma group with **EGFR** gene amplification (8 tumours, median value of Ki-67 LI 4.2, range 0.4-24.6) than in those without **EGFR** gene amplification (12 tumours, median value of Ki-67 LI 0.8 range 0.2-11.8) (0.05 p lt 0.01). The glioblastoma patients with Ki-67 LI gt 1.5 (10 tumours) had a statistically significant shorter survival than those with Ki-67 LI KAPPA 1.5 (10 tumours) (p lt 0.05). The glioblastoma patients with **EGFR** gene amplification, lived shorter time than those without **EGFR** gene amplification (p gt 0.05).

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=> s antibod?
L10    2980692 ANTIBOD?

=> s l10 and ErbB1
L11         459 L10 AND ERBB1

=> s l11 and EGFR
L12         151 L11 AND EGFR

=> s l12 combination
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L13 39 L12 AND COMBINATION

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PROCESSING COMPLETED FOR L13
L14 15 DUP REMOVE L13 (24 DUPLICATES REMOVED)

=> d l14 1-15 cbib abs

L14 ANSWER 1 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:303341 Document No.: PREV200700308469. The **combination** of lapatinib (GW572016F) and agents targeting the insulin-like growth factor I receptor results in synergistic tumor cell growth inhibition and induction of apoptosis. Rusnak, David W. [Reprint Author]; Kumar, Rakesh; Gilmer, Tona M.. GlaxoSmithKline Inc, Res Triangle Pk, NC USA. Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2007) Vol. 48, pp. 1357.
Meeting Info.: 98th Annual Meeting of the American-Association-for-Cancer-Research. Los Angeles, CA, USA. April 14 -18, 2007. Amer Assoc Canc Res.
ISSN: 0197-016X. Language: English.

L14 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1
2007075608. PubMed ID: 17208435. Dual inhibition of **ErbB1** (**EGFR**/HER1) and ErbB2 (HER2/neu). Reid Alison; Vidal Laura; Shaw Heather; de Bono Johann. (Royal Marsden Hospital, The Institute of Cancer Research, Centre for Cancer Therapeutics, Downs Road, Sutton, Surrey SM2 5PT, UK.) European journal of cancer (Oxford, England : 1990), (2007 Feb) Vol. 43, No. 3, pp. 481-9. Electronic Publication: 2007-01-08. Ref: 82.
Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.
AB Targeting of epidermal growth factor receptor (**EGFR**) and HER2 is a proven anti-cancer strategy. However, heterodimerisation, compensatory 'crosstalk' and redundancy exist in the ErbB network, and there is therefore a sound scientific rationale for dual inhibition of **EGFR** and HER2. Trials of approved agents in **combination**, for example trastuzumab and cetuximab, are underway. There is also a new generation of small molecule tyrosine kinase inhibitors (TKIs) and monoclonal **antibodies** (mABs) that target two or more ErbB receptors. Lapatinib, a TKI of **EGFR** and HER2, has shown clinical benefit in trastuzumab refractory breast cancer and is poised for FDA approval. Other agents include BIBW-2992 and HKI-272, irreversible TKIs of **EGFR** and HER2, and pertuzumab, a heterodimerisation inhibitor of **EGFR** and HER2.

L14 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
2007098583. PubMed ID: 16738850. Efficient inhibition of **EGFR** signaling and of tumour growth by antagonistic anti-EFGR Nanobodies. Roovers Rob C; Laeremans Toon; Huang Lieven; De Taeye Severine; Verkleij Arie J; Revets Hilde; de Haard Hans J; van Bergen en Henegouwen Paul M P. (Department of Molecular Cell Biology, Institute of Biomembranes, Utrecht University, Padualaan 8, CH-3584 Utrecht, The Netherlands.) Cancer immunology, immunotherapy : CII, (2007 Mar) Vol. 56, No. 3, pp. 303-317.
Journal code: 8605732. ISSN: 0340-7004. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB The development of a number of different solid tumours is associated with over-expression of **ErbB1**, or the epidermal growth factor receptor (**EGFR**), and this over-expression is often correlated with poor prognosis of patients. Therefore, this receptor tyrosine kinase is considered to be an attractive target for **antibody**-based therapy. Indeed, **antibodies** to the **EGFR** have already proven their value for the treatment of several solid tumours, especially in **combination** with chemotherapeutic treatment regimens. Variable domains of camelid heavy chain-only **antibodies** (called Nanobodies) have superior properties compared with classical

antibodies in that they are small, very stable, easy to produce in large quantities and easy to re-format into multi-valent or multi-specific proteins. Furthermore, they can specifically be selected for a desired function by phage **antibody** display. In this report, we describe the successful selection and the characterisation of antagonistic anti-**EGFR** Nanobodies. By using a functional selection strategy, Nanobodies that specifically competed for EGF binding to the **EGFR** were isolated from "immune" phage Nanobody repertoires. The selected **antibody** fragments were found to efficiently inhibit EGF binding to the **EGFR** without acting as receptor agonists themselves. In addition, they blocked EGF-mediated signalling and EGF-induced cell proliferation. In an in vivo murine xenograft model, the Nanobodies were effective in delaying the outgrowth of A431-derived solid tumours. This is the first report describing the successful use of untagged Nanobodies for the in vivo treatment of solid tumours. The results show that functional phage **antibody** selection, coupled to the rational design of Nanobodies, permits the rapid development of novel anti-cancer **antibody**-based therapeutics.

L14 ANSWER 4 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007012849 EMBASE HER-2 and NF-κB as the targets for therapy-resistant breast cancer. Ahmed K.M.; Cao N.; Li J.J.. Dr. J.J. Li, 1279 Civil Engineering Building, 550 Stadium Mall Drive, West Lafayette, IN 47907, United States. jjli@purdue.edu. Anticancer Research Vol. 26, No. 6 B, pp. 4235-4243 2006.
Refs: 106.
ISSN: 0250-7005. CODEN: ANTRD4
Pub. Country: Greece. Language: English. Summary Language: English.
Entered STN: 20070130. Last Updated on STN: 20070130

AB HER-2 (also called ErbB2 or Neu) tyrosine kinase, one of the four members of ErbB receptor family (**ErbB1**, i.e., **EGFR**, ErbB2, ErbB3 and ErbB4), plays a critical role in the control of diverse cellular functions involved in differentiation, proliferation, migration and cell survival via multiple signal transduction pathways. Overexpression of HER-2, observed in HER-2-positive breast cancer patients, is believed to cause the tumor resistance to an array of anti-cancer agents and poor prognosis. Although HER-2 **antibodies** have shown growth inhibitory effects, more efficient molecular targets against HER-2-mediated tumor resistance need to be developed. The molecular mechanisms underlying HER-2-mediated tumor resistance, especially the connections between HER-2 and therapy-resistant signaling networks, need to be further investigated. NF-KB, a key stress transcription factor that can initiate a pro-survival network, was found to be activated in many cancer cells overexpressing HER-2 and to be responsible for the radiation resistance in HER-2 transfected breast cancer cells. Recent findings in literature and data from this laboratory suggest a possible co-operation between HER-2 and NF-κB in signaling tumor resistance to radiotherapy. This review will discuss the mechanisms of HER-2 mediated NF-κB signaling pathway and potential target for therapeutic intervention.

L14 ANSWER 5 OF 15 MEDLINE on STN DUPLICATE 3

2006581555. PubMed ID: 16858684. Peptabody-EGF: a novel apoptosis inducer targeting **ErbB1** receptor overexpressing cancer cells. Fattah Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R; Mach Jean Pierre; Deperthes David. (Department of Urology, Urology Research Unit, CHUV, Epalinges, Switzerland.) International journal of cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10, pp. 2455-63. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The epidermal growth factor receptor (**EGFR**) plays a central role in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial

malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of **EGFR** represents a very promising challenge in oncology, and **antibodies** raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such **antibodies**, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or **combinations** thereof. We report here the development of an alternative high affinity molecule that is directed against **EGFR**. Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of **EGFR**. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing **EGFR**. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal **EGFR antibody** Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on **EGFR** overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-**EGFR** therapy.

L14 ANSWER 6 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006266133 EMBASE EGF receptor mutations in lung cancer: From humans to mice and maybe back to humans. Arteaga C.L.. C.L. Arteaga, Departments of Medicine and Cancer Biology, Breast Cancer Research Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, United States. carlos.arteaga@vanderbilt.edu. Cancer Cell Vol. 9, No. 6, pp. 421-423 13 Jun 2006.
Refs: 23.
ISSN: 1535-6108. CODEN: CCAECI
S 1535-6108(06)00151-6. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060706. Last Updated on STN: 20060706

AB Deletions in exon 19 and nucleotide substitutions in exon 21 are the most common mutations of the **EGFR** (**ErbB1**) in NSCLC. These mutations endow the receptor with constitutive kinase activity. Most tumors expressing these mutants respond well to **EGFR** tyrosine kinase inhibitors, suggesting that they are dependent on mutant **EGFR** signaling. Two groups developed transgenic mice in which expression of these mutants is temporally induced in mouse lung. Mice expressing **EGFR** mutants develop bronchioloalveolar cancer and lung adenocarcinoma, which are highly sensitive to **EGFR** inhibitors. These mouse models provide important opportunities for studying the biology of NSCLC and the refinement of anti-**EGFR** therapies. .COPYRGT. 2006 Elsevier Inc. All rights reserved.

L14 ANSWER 7 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006374473 EMBASE The complexity of targeting **EGFR** signalling in cancer: From expression to turnover. Sebastian S.; Settleman J.; Reshkin S.J.; Azzariti A.; Bellizzi A.; Paradiso A.. A. Paradiso, Clinical Experimental Oncology Laboratory, National Cancer Institute, Via Amendola, 209, 70126 Bari, Italy. a.paradiso@oncologico.bari.it. Biochimica et Biophysica Acta - Reviews on Cancer Vol. 1766, No. 1, pp. 120-139 2006.
Refs: 250.
ISSN: 0304-419X. CODEN: BBACEU
S 0304-419X(06)00032-1. Pub. Country: Netherlands. Language: English.

Summary Language: English.
Entered STN: 20060824. Last Updated on STN: 20060824

AB The epidermal growth factor receptor (**ErbB1** or **EGFR**) has been found to be altered in a variety of human cancers. A number of agents targeting these receptors, including specific **antibodies** directed against the ligand-binding domain of the receptor and small molecules that inhibit kinase activity are either in clinical trials or are already approved for clinical treatment. However, identifying patients that are likely to respond to such treatments has been challenging. As a consequence, it still remains important to identify additional alterations of the tumor cell that contribute to the response to **EGFR**-targeted agents. While **EGFR**-mediated signalling pathways have been well established, there is still a rather limited understanding of how intracellular protein-protein interactions, ubiquitination, endocytosis and subsequent degradation of **EGFR** contribute to the determination of sensitivity to **EGFR** targeting agents and are emerging areas of investigation. This review primarily focuses on the basic signal transduction pathways mediated through activated membrane bound and/or endosomal **EGFR** and emphasizes the need to co-target additional proteins that function either upstream or downstream of **EGFR** to improve cancer therapy.

L14 ANSWER 8 OF 15 SCISEARCH

2005:579387 The Genuine Article (R) Number: 930JI. Clinical applications for targeted therapy in bladder cancer. Adam L; Kassouf W; Dinney C P N (Reprint). Univ Texas, MD Anderson Canc Ctr, Dept Urol, 1515 Holcombe Blvd, Unit 1373, Houston, TX 77030 USA (Reprint); Univ Texas, MD Anderson Canc Ctr, Dept Urol, Houston, TX 77030 USA; Univ Texas, MD Anderson Canc Ctr, Dept Canc Biol, Houston, TX 77030 USA. cdinney@mdanderson.org. UROLOGIC CLINICS OF NORTH AMERICA (MAY 2005) Vol. 32, No. 2, pp. 239-+. ISSN: 0094-0143. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Transitional cell carcinoma (TCC) of the bladder is the fourth most common solid-tumor malignancy in men in the United States. Approximately 17,060 men in the United States died from TCC of the bladder in 2004; most of the deaths were due to metastatic disease [1]. Metastatic TCC is usually treated with systemic chemotherapy, including regimens such as M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) (2-4]. However, despite systemic chemotherapy with even the most effective regimens, most patients with distant metastatic bladder cancer die of the disease after a median survival duration of 18 months [3,4]. Although considerable efforts have been made to escalate the dose of MNAC, to modulate the components of the regimens, and to use novel **combination** regimens that include active agents such as paclitaxel, gemcitabine, and ifosfamide, there has been no improvement in survival [5-10]. Although some of these newer regimens produce fewer toxic side effects than MNAC, there is yet no compelling evidence that they improve patient survival. In general, the treatment of metastatic TCC of the bladder by classic cytotoxic chemotherapy has reached a therapeutic plateau. Despite high rates of response to treatment, the disease is generally incurable. However, it is clear that cytotoxic chemotherapy has provided significant palliation for many patients, and has resulted in improved outcome, probability for cure, or both in the adjuvant setting of microscopic metastatic disease.

Although chemotherapy is still an important component of combined therapy, the need for more effective treatment options exists. Fortunately, an improved understanding of the biology of malignancy is finally facilitating the design of novel therapeutic approaches to battle cancer. Urothelial transformation involves several cellular events including the deregulation of cellcycle and apoptotic pathways via mutation or altered expression of p53, p21/WAF-1, pRB, p27, and INK4A

(p16). Progression of urothelial carcinoma has also been related to various members of the erbB family, vascular epidermal growth factor (VEGF), nerve factor-kappa B (NF kappa B), Akt, PTEN, and cyclooxygenase/2 (COX-2) [11]. All of these molecules are potential targets for novel therapies. The focus of this article is the aberrant signal transduction of members of the erbB family (ie, epidermal growth factor receptor [**EGFR**], and human epidermal growth factor receptors [HER]-2, -3, and -4) in TCC of the bladder. **EGFR** was sequenced and cloned by Ullrich in 1984 [12]. **EGFR**, HER1, or c-**erbB1**, is the prototype of the type I receptor tyrosine kinase (RTK) family, which also includes HER2 (cerbB2), HER3 (c-erbB-3), and HER4 (c-erbB-4) [13-15]. **EGFR** family members transmit the biologic effects of the EGF family of ligands, which includes EGF, transforming growth factor-alpha (TGF alpha), amphiregulin, heparin-binding (HB)-EGF, betacellulin, and epiregulin. Ligand binding induces the formation of homodimers or heterodimers between **EGFR** and other members of this family, autophosphorylation of tyrosine residues in its intracellular domain, and activation of downstream signaling pathways [13-15]. These phosphotyrosines, in turn, phosphorylate other intracellular proteins that contain src homologous domains (SH2 and SH3), such as ras-associated GTPase activating protein, phosphatidylinositol3-kinase, and phospholipase C gamma. The downstream signaling pathways activated by these intracellular proteins include the ras/raf MAPKinase, phosphatidylinositol-3-kinase, and protein kinase C pathways, which ultimately lead to increased nuclear transcription and subsequent cellular proliferation [15,16]. Overexpression of **EGFR** alone or accompanied by production of one or more of its ligands, such as TGF alpha, has been reported in a range of human malignancies and is often associated with poor prognosis [16,17]. Overexpression of **EGFR** in bladder cancer has been widely reported [1823]. The reports suggest the presence of **erbB1** in 23% to 100% of TCC samples. Several studies have shown that **EGFR** is positively associated with advanced tumor stage, tumor progression, and poor clinical outcome [24]. Immunohistochemical analyses suggest that rather than actual overexpression of **erbB1** in TCC is the actual change in the distribution of the molecule, from basal layer in normal urothelium to all layers in premalignant or malignant urotheliums [25,26]. Other studies have demonstrated that expression of **erbB1** and of erbB2 is downregulated in TCC compared with the expression in normal urothelium [27]. Still other studies have demonstrated erbB3 in 20% to 56% and erbB4 in 11% to 30% of cases of TCC, but reduced expression of erbB3 and erbB4 in TCC compared with normal tissues [27]. Statistical analyses of erbB expression patterns and clinical parameters have resulted in varying conclusions about the prognostic significance of erbB expression in TCC [27-32].

However, in patients with muscle-invasive TCC of the bladder, a retrospective immunohistochemical study has shown erbB2 overexpression to be a independent predictor of reduced cancer-specific survival [33]. In contrast, another prospective study found that erbB2 overexpression in the context of paclitaxel-based chemotherapy significantly decreased the risk of death [34]. On the basis of discovery of variant isoforms of the erbB family members, a series of studies was initiated that focused on acquiring quantitative information about erbB status, which was considered critical for selecting patients for erbB inhibitor therapies, and for evaluating the potential use of erbBs as prognostic indicators for patients with cancer. A report by Juntilla et al [35] describing specific erbB4 cytoplasmic or juxtamembrane isoforms overexpressed in TCC compared with its expression in interstitial cystitis or normal bladder, is an example of such finding. Thus, preclinical evidence about the expression levels of specific erbBs in TCC tissues, although controversial at the moment, may be verified through a more refined investigation. Several erbB I variants, somatic mutations, deletions, or truncations have been described for **erbB1** in epithelial cancers, including lung, colon, and breast cancers [36-39]. For example, the erbBvIII variant, which lacks the extracellular domain, has been shown to be specifically

expressed in tumor tissues rather than in normal, adjacent tissues and to activate aberrant signaling pathways relevant for **EGFR**-targeted therapy [40,41]. However, there currently are no studies investigating this aspect in bladder cancer.

L14 ANSWER 9 OF 15 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:387361 The Genuine Article (R) Number: 912JF. Characterization of HER1 (c-**erbB1**) status in locally advanced breast cancer using fluorescence in situ hybridization and immunohistochemistry. Corzo C (Reprint); Tusquets I; Salido M; Corominas J M; Bellet M; Suarez M; Baro T; Fabregat X; Serrano S; Sole F. Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, Pg Maritim 25-29, ES-08003 Barcelona, Spain (Reprint); Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, ES-08003 Barcelona, Spain; Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Med Oncol Serv, ES-08003 Barcelona, Spain; Univ Autonoma Barcelona, Dept Biol Cellular Fisiol & Immunol, E-08193 Barcelona, Spain. E0062@imas.imim.es. TUMOR BIOLOGY (2005) Vol. 26, No. 1, pp. 25-30. ISSN: 1010-4283. Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Epidermal growth factor receptor (**EGFR**) is a 170-kDa transmembrane glycoprotein encoded by the HER1 protooncogene, located at 7p12. This receptor is related to the pathogenesis of breast cancer. The aim of this study was to analyze the status of HER1 using fluorescence in situ hybridization (FISH) and immunohistochemistry in a series of 48 patients with locally advanced breast cancer (LABC). Before neoadjuvant chemotherapy, core biopsies were taken from patients with LABC and were processed into paraffin blocks. Biopsies were then studied using FISH with a HER1 probe (Vysis, Downers Grove, Ill., USA). They were also analyzed immunohistochemically using two different **EGFR** **antibodies** from DakoCytomation (Denmark, A/S) and from Zymed (San Francisco, Calif., USA). HER1 amplifications were not found, although 31% of the cases presented aneusomy of chromosome 7. Only 2 cases presented **EGFR** expression. LABC presented a low level of **EGFR** expression. HER1 amplification was not present in LABC, although the polysomy of chromosome 7 was a common finding. Copyright (C) 2005 S. Karger AG, Basel.

L14 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2004:404840 Document No. 142:129837 Anti-**EGFR**-mediated radiosensitization as a result of augmented **EGFR** expression. Bonner, James A.; Buchsbaum, Donald J.; Russo, Suzanne M.; Fiveash, John B.; Trummell, Hoa Q.; Curiel, David T.; Raisch, Kevin P. (Department of Radiation Oncology, Univ. Alabama Sch Med., Birmingham, AL, USA). International Journal of Radiation Oncology, Biology, Physics, 59(2, Suppl.), 2-10 (English) 2004. CODEN: IOBPD3. ISSN: 0360-3016. Publisher: Elsevier Science Inc..

AB Elevated epidermal growth factor receptor (**EGFR**) expression has correlated with a poor prognosis after standard treatment of several malignancies. However, it is not clear whether the absolute level of **EGFR** expression affects the radiosensitizing properties of anti-**EGFR** treatments. A better understanding of this question would be helpful for the design of protocols that deliver these treatments. To explore this question, cells (LS174T) that did not display inherent anti-**EGFR** treatment-induced radiosensitization were selected for studies that could potentially enhance **EGFR** expression. Human colon carcinoma cells (LS174T), which did not show radiosensitization by anti-**EGFR** treatments, were employed for these studies. (Also, these cells were not responsive to the antiproliferative effects of anti-**EGFR** treatment.). Using standard transfection techniques (eukaryotic expression vector) as well as an adenoviral construct to enhance **EGFR** expression, LS174T cells were transduced in a manner that resulted in enhanced expression of **EGFR**. Subsequently, standard

proliferation studies were performed to test the radiosensitizing properties of anti-**EGFR** treatment (an anti-**EGFR** monoclonal **antibody**: IMC-C225). Studies were undertaken to stably transfect LS174T cells with **EGFR**. The stable transfectants, LS174T.**EGFR** cells, were responsive to the antiproliferative effects of anti-**EGFR** treatment, in contrast to the parent LS174T cells. Similar results were demonstrated when the cells were infected with AdEGFR. Addnl., the LS174T.**EGFR** cells were responsive to the radiosensitizing properties of anti-**EGFR** treatment (IMC-C225), whereas the parent cells were not. Although the level of **EGFR** expression is of prognostic significance in many tumor models, the response of cells to anti-**EGFR** treatment alone, or **combinations** of this treatment with radiation or chemotherapy, depends upon many factors that are not necessarily related to the inherent **EGFR** expression of the tumor cells. However, the studies reported herein, demonstrate that when LS174T cells were transduced to show increased **EGFR** expression, they became responsive to the radiosensitizing properties of anti-**EGFR** treatments.

L14 ANSWER 11 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003257887 EMBASE Gene products involved in metastasis of bladder cancer. Davies B.R.. Dr. B.R. Davies, Schl. of Surg. and Reproductive Sci., University of Newcastle, Medical School, Newcastle-Upon-Tyne NE2 4HH, United Kingdom. B.R.Davies@ncl.ac.uk. Histology and Histopathology Vol. 18, No. 3, pp. 969-980 2003.
Refs: 104.
ISSN: 0213-3911. CODEN: HIHIES
Pub. Country: Spain. Language: English. Summary Language: English.
Entered STN: 20030717. Last Updated on STN: 20030717

AB Metastasis is usually responsible for mortality in patients suffering from muscle invasive bladder cancer. Whilst expression of a great number of genes and their protein products have been associated with metastasis and/or poor prognosis in bladder cancer, evidence that they actively drive the metastatic process, and hence make potentially good therapeutic targets, is often lacking. This is due to the limited number and application of effective animal models which reflect the pathogenesis of the human disease. In this review I will discuss the processes involved in metastasis, consider the established animal models of bladder cancer progression and metastasis, and review the evidence for a role of various gene products in this process. Consideration of clinical studies in conjunction with evidence from experimental animal models reveals that the tyrosine kinase receptor **erbB1/EGFR**, the calcium binding protein S100A4 and the the cell cycle arrest/apoptosis-inducing p53 protein are amongst the most promising targets for therapy against metastatic disease in patients with bladder cancer.

L14 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 4

2003134501. PubMed ID: 12648471. ErbB-targeted therapeutic approaches in human cancer. Arteaga Carlos L. (Department of Medicine, Vanderbilt University School of Medicine, and Breast Cancer Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, USA.. arlos.artega@vanderbilt.edu) . Experimental cell research, (2003 Mar 10) Vol. 284, No. 1, pp. 122-30. Ref: 100. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB The overexpression and aberrant function of the epidermal growth factor receptor (**EGFR**, **erbB1**, HER1) and its ligands and coreceptors in a wide spectrum of epithelial cancers have provided a rationale for targeting this signaling network with novel treatment approaches. Several antireceptor therapeutic strategies have been pursued, but two stand ahead in their clinical development. One approach has been the generation of small molecules that compete with adenosine triphosphate (ATP) for binding to the receptor's kinase pocket, thus blocking receptor activation and the transduction of postreceptor signals.

The second approach utilizes humanized monoclonal **antibodies** generated against the receptor's ligand-binding extracellular domain. These **antibodies** block binding of receptor-activating ligands and, in some cases, can induce receptor endocytosis and downregulation. Clinical studies already suggest that both of these approaches, either alone or in **combination** with standard anticancer therapies, are well tolerated and can induce clinical responses and tumor stabilization in a variety of common carcinomas.

L14 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2003:143026 Document No. 139:209971 **Combination** of epidermal growth factor receptor targeted therapy with radiation therapy for malignant gliomas. Krishnan, Sunil; Rao, Ravi D.; James, C. David; Sarkaria, Jann N. (Department of Oncology, Mayo Clinic and Foundation, Rochester, MN, USA). Frontiers in Bioscience, 8, E1-E13 (English) 2003. CODEN: FRBIF6. ISSN: 1093-4715. URL: http://WWW.bioscience.org/2003/v8/e/895/pdf.pdf Publisher: Frontiers in Bioscience.

AB A review. Glioblastoma multiform (GBM) are extremely aggressive brain tumors characterized by resistance to standard treatment modalities including surgery, radiation therapy and chemotherapy. While radiation therapy is the standard treatment after surgical resection, these tumors invariably recur and are associated with a uniformly dismal prognosis. Cytotoxic chemotherapy has failed to improve on the modest gains conferred by radiation therapy. Our understanding of the mol. events driving glioma-genesis has led to the recognition of frequent alterations in the epidermal growth factor receptor (**EGFR**) pathway, leading to increased aggressiveness and a poorer prognosis. Based on the importance of **EGFR** in the development of malignancy in multiple tumor types, several classes of novel therapeutic agents have been developed that specifically target **EGFR**. This review outlines the relevance of normal and aberrant **EGFR** signaling in the biol. of gliomas, the strategies for inhibiting **EGFR** activity and the rationale for combining **EGFR** inhibitors with radiation therapy in the treatment of GBM.

L14 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 5
2002046609. PubMed ID: 11751413. Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/neu (erbB2)-overexpressing breast cancer cells in vitro and in vivo. Moulder S L; Yakes F M; Muthuswamy S K; Bianco R; Simpson J F; Arteaga C L. (Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6307, USA.) Cancer research, (2001 Dec 15) Vol. 61, No. 24, pp. 8887-95. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Aberrrant signaling by the epidermal growth factor receptor [**EGFR** (HER1, **erbB1**)] and/or HER2/neu tyrosine kinases is present in a cohort of breast carcinomas. Because HER2 is constitutively phosphorylated in some breast tumors, we speculated that, in these cancers, transmodulation of HER2 may occur via **EGFR** signaling. To test this possibility, we examined the effect of **EGFR** -specific kinase inhibitors against the HER2-overexpressing human breast tumor lines BT-474, SKBR-3, MDA-361, and MDA-453. ZD1839 (Iressa) is an ATP-mimetic that inhibits the purified **EGFR** and HER2 kinases in vitro with an IC(50) of 0.033 and >3.7 microM, respectively. The specificity of ZD1839 against **EGFR** was confirmed in Rat1 fibroblasts transfected with **EGFR** or HER2 chimeric receptors activated by synthetic ligands without the interference of endogenous receptors. Treatment of all breast cancer cell lines (except MDA-453) with 1 microM ZD1839 almost completely eliminated HER2 phosphorylation. In contrast, the incorporation of [gamma-(32)P]ATP in vitro onto HER2 receptors isolated from BT-474 cells was unaffected by 1 microM ZD1839. **EGFR** is expressed by BT-474, SKBR-3, and MDA-361 but not by MDA-453 cells, suggesting that ZD1839-mediated inhibition of the **EGFR** kinase explained the inhibition of HER2 phosphorylation in vivo. In SKBR-3 cells, ZD1839 exhibited a greater growth-inhibitory effect than Herceptin, a monoclonal **antibody** against the HER2

ectodomain. In both SKBR-3 and BT-474 cells, treatment with ZD1839 plus Herceptin induced a greater apoptotic effect than either inhibitor alone. Finally, ZD1839 completely prevented growth of BT-474 xenografts established in nude mice and enhanced the antitumor effect of Herceptin. These data imply that **EGFR** tyrosine kinase inhibitors will be effective against HER2-overexpressing breast tumor cells that also express **EGFR** and support their use in **combination** with HER2 **antibodies**, such as Herceptin, against mammary carcinomas with high levels of the HER2 proto-oncogene.

L14 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 6
2001098135. PubMed ID: 11156523. Molecular mechanisms underlying ErbB2/HER2 action in breast cancer. Harari D; Yarden Y. (Department of Biological Regulation, the Weizmann Institute of Science, Rehovot, Israel.) Oncogene, (2000 Dec 11) Vol. 19, No. 53, pp. 6102-14. Ref: 198. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Overexpression of ErbB2, a receptor-like tyrosine kinase, is shared by several types of human carcinomas. In breast tumors the extent of overexpression has a prognostic value, thus identifying the oncoprotein as a target for therapeutic strategies. Already, **antibodies** to ErbB2 are used in **combination** with chemotherapy in the treatment of metastasizing breast cancer. The mechanisms underlying the oncogenic action of ErbB2 involve a complex network in which ErbB2 acts as a ligand-less signaling subunit of three other receptors that directly bind a large repertoire of stroma-derived growth factors. The major partners of ErbB2 in carcinomas are **ErbB1** (also called **EGFR**) and ErbB3, a kinase-defective receptor whose potent mitogenic action is activated in the context of heterodimeric complexes. Why ErbB2-containing heterodimers are relatively oncopotent is a function of a number of processes. Apparently, these heterodimers evade normal inactivation processes, by decreasing the rate of ligand dissociation, internalizing relatively slowly and avoiding the degradative pathway by returning to the cell surface. On the other hand, the heterodimers strongly recruit survival and mitogenic pathways such as the mitogen-activated protein kinases and the phosphatidylinositol 3-kinase. Hyper-activated signaling through the ErbB-signaling network results in dysregulation of the cell cycle homeostatic machinery, with upregulation of active cyclin-D/CDK complexes. Recent data indicate that cell cycle regulators are also linked to chemoresistance in ErbB2-dependent breast carcinoma. Together with D-type cyclins, it seems that the CDK inhibitor p21waf1 plays an important role in evasion from apoptosis. These recent findings herald a preliminary understanding of the output layer which connects elevated ErbB-signaling to oncogenesis and chemoresistance.

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L15 ANSWER 1 OF 1 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2006500693 EMBASE Peptabody-EGF: A novel apoptosis inducer targeting **ErbB1** receptor overexpressing cancer cells. Fattah O.M.; Cloutier S.M.; Kundig C.; Felber L.M.; Gygi C.M.; Jichlinski P.; Leisinger H.-J.; Gauthier E.R.; Mach J.P.; Deperthes D.. D. Deperthes, Urology Research Unit/Med Discovery S.A., Biopole, Ch. Croisettes 22, CH-1066 Epalinges, Switzerland. david.deperthes@med-discovery.com. International Journal of Cancer Vol. 119, No. 10, pp. 2455-2463 15 Nov 2006.
Refs: 29.
ISSN: 0020-7136. E-ISSN: 1097-0215. CODEN: IJCNAW
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20061027. Last Updated on STN: 20061027

AB The epidermal growth factor receptor (**EGFR**) plays a central role

in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of **EGFR** represents a very promising challenge in oncology, and **antibodies** raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such **antibodies**, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or combinations thereof. We report here the development of an alternative high affinity molecule that is directed against **EGFR.** Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of **EGFR.** Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing **EGFR.** However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal **EGFR antibody** Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on **EGFR** overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-**EGFR** therapy. .COPYRGT. 2006 Wiley-Liss, Inc.

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L17  ANSWER 1 OF 3     MEDLINE on STN                    DUPLICATE 1
2006581555.     PubMed ID: 16858684.   Peptabody-EGF: a novel apoptosis inducer
      targeting ErbB1 receptor overexpressing cancer cells. Fattah
      Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi
      Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R;
      Mach Jean Pierre; Deperthes David. (Department of Urology, Urology
      Research Unit, CHUV, Epalinges, Switzerland. ) International journal of
      cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10,
      pp. 2455-63.  Journal code: 0042124. ISSN: 0020-7136. Pub. country: United
      States. Language: English.
AB    The epidermal growth factor receptor (EGFR) plays a central role in cell
      life by controlling processes such as growth or proliferation. This
      receptor is commonly overexpressed in a number of epithelial malignancies
      and its upregulation is often associated with an aggressive phenotype of
      the tumor. Thus, targeting of EGFR represents a very promising challenge
      in oncology, and antibodies raised against this receptor have
      been investigated as potential antitumor agents. Various putative
      mechanisms of action were proposed for such antibodies,
      including decreased proliferation, induction of apoptosis, stimulation of
      the immunological response against targeted cancer cells or combinations
      thereof. We report here the development of an alternative high affinity
      molecule that is directed against EGFR. Production of this pentameric
      protein, named peptabody-EGF, includes expression in a bacterial
      expression system and subsequent refolding and multimerization of
      peptabody monomers. The protein complex contains 5 human EGF ligand
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domains, which confer specific binding towards the extracellular portion of EGFR. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing EGFR. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal EGFR **antibody Mab-425**. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than **antibody** mediated effects when tested on EGFR overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-EGFR therapy.

L17 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB **antibodies** and their use in tumor therapy. Kreysch, Hans-Georg (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.

AB The invention relates to novel bispecific **antibodies** and their use in tumor therapy. The novel **antibodies** have the ability to bind to ErbB receptors, preferably **ErbB1** receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these **antibodies** are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal **antibodies MAb 425** and chimeric MAb 225 was presented.

L17 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. Kreysch, Hans-Georg; Schmidt, Juergen (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal **antibodies** (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred **antibodies** according to this invention are **MAb 425** and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for **antibody**-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two **antibodies** with specificity for different epitopes of the human

EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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L23 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. **Kreysch, Hans-Georg**; **Schmidt, Juergen** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal **antibodies** (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred **antibodies** according to this invention are MAb 425 and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for **antibody**-dependent cell-mediated cytotoxicity was investigated using **EGFR** pos. A431 target cells and two **antibodies** with specificity for different epitopes of the human **EGFR** (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

L23 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2003:502686 Document No.: PREV200300498451. The humanized monoclonal anti-**EGFR antibody** EMD72000 potently inhibits the growth of **EGFR**-expressing human tumor xenografts insensitive to chemotherapeutic drugs. Burger, Angelika M. [Reprint Author]; Heiss, Nina S.; **Kreysch, Hans-Georg**; Schandelmaier, Kathrin; Wirth, Gregory; Fiebig, Heinz H.; Grell, Matthias. Oncotest, Freiburg, Germany. Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 1139. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer

Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X. Language: English.

L23 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2002:539555 Document No. 137:108304 Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting **antibodies** and angiogenesis inhibitors for treating cancer and metastasis. Goodman, Simon; **Kreysch, Hans-Georg** (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2002055106 A2 20020718, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP15241 20011221. PRIORITY: EP 2001-100507 20010109.

AB The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of receptor tyrosine kinase antagonists/inhibitors, especially ErbB receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or radiation therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone.

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L25 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB **antibodies** and their use in tumor therapy. **Kreysch, Hans-Georg** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.

AB The invention relates to novel bispecific **antibodies** and their use in tumor therapy. The novel **antibodies** have the ability to bind to ErbB receptors, preferably **ErbB1** receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these **antibodies** are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal **antibodies** MAb 425 and chimeric MAb 225 was presented.

L25 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. **Kreysch, Hans-Georg**; **Schmidt, Juergen** (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal **antibodies** (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred **antibodies** according to this invention are MAb 425 and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for **antibody**-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two **antibodies** with specificity for different epitopes of the human EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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L27 ANSWER 1 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2007060458 EMBASE Four Cases of Sirolimus-Associated Interstitial Pneumonitis: Identification of Risk Factors. Morath C.; Schwenger V.; Ksoll-Rudek D.; Sommerer C.; Beimler J.; **Schmidt J.**; Zeier M..
C. Morath, Department of Nephrology, University of Heidelberg, Heidelberg, Germany. christian_morath@med.uni-heidelberg.de. Transplantation Proceedings Vol. 39, No. 1, pp. 99-102 2007.
Refs: 21.
ISSN: 0041-1345. CODEN: TRPPA8
S 0041-1345(06)01482-5. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070319. Last Updated on STN: 20070319

AB Sirolimus-associated interstitial pneumonitis is a severe side effect of sirolimus therapy; fatal outcomes have been described. We report 4 patients with sirolimus-associated interstitial pneumonitis and review the literature for risk factors for the development of disease. Until June 2005, 48 patients received either de novo sirolimus treatment (n = 7) or were switched from a calcineurin inhibitor-containing regimen to a sirolimus-based protocol for various indications (n = 41). Compared with the 44 patients on sirolimus therapy with no evidence of a disorder, the 4 patients (8.3%) who developed suspected sirolimus-associated interstitial pneumonitis showed no difference in gender, immunosuppressive therapy, days posttransplantation, comorbidity, or preexistent lung disease. Several points, however, are of interest. None of the de novo-treated patients except 4 patients (9.8%) with late administration of sirolimus developed interstitial pneumonitis. The 4 patients with interstitial

pneumonitis tended to be older (58.7 ± 5.5 vs 46.9 ± 1.7 years) and received higher sirolimus doses (3.5 ± 0.5 vs 1.4 ± 0.2 mg/d) with greater trough levels (15.4 ± 2.9 vs 8.0 ± 1.2 μg/L) at the onset of symptoms. Most notably, all patients with interstitial pneumonitis had a loading dose at the start of therapy, and an increase in sirolimus dose (or trough level) within 3 weeks prior to the onset of symptoms. Additional potential risk factors identified from the literature include allograft dysfunction, hypervolemia, and male gender. With careful monitoring (or even exclusion from therapy) of patients at risk for the development of disease, we have had no case of sirolimus-associated interstitial pneumonitis since September 2004.

L27 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

2006:1070279 Document No. 145:410678 Methods for treating infectious disease exacerbated asthma using CpG oligonucleotides. Krieg, Arthur M.; De Sanctis, George Tilo; Underwood, Stephen Leslie; Jupp, Raymond Anthony; **Schmidt, John A.** (Coley Pharmaceutical Group, Inc., USA; Sanofi-Aventis U.S.P. LLC). U.S. Pat. Appl. Publ. US 2006229271 A1 20061012, 60pp. (English). CODEN: USXXCO. APPLICATION: US 2006-401093 20060410. PRIORITY: US 2005-669548P 20050408.

AB It has been discovered herein that CpG oligonucleotides (CpG ODN) are particularly effective in combating infections, and particularly upper respiratory tract virus, that are a cause of asthma exacerbations. In some aspects of the invention C-class CpG ODN are particularly effective for carrying out the methods. As shown in the Examples below, C-class CpG ODN induced a panel of IFN-associated genes in the mouse, including those for antiviral proteins, and protected against airway inflammation exacerbated by combined antigen and virus exposures.

L27 ANSWER 3 OF 14 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:1051354 The Genuine Article (R) Number: 096WU. PEG-hirudin/iloprost coating of small diameter ePTFE grafts effectively prevents pseudointima and intimal hyperplasia development. Heise M (Reprint); Schmidmaier G; Husmann I; Heidenhain C; **Schmidt J**; Neuhaus P; Settmacher U. Univ Med, Charite, Dept Gen Surg, Augustenburger Pl 1, D-13353 Berlin, Germany (Reprint); Univ Med, Charite, Dept Gen Surg, D-13353 Berlin, Germany; Charite, Ctr Musculoskeletal Surg, D-13353 Berlin, Germany. michael.heise@charite.de. EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY (OCT 2006) Vol. 32, No. 4, pp. 418-424. ISSN: 1078-5884. Publisher: W B SAUNDERS CO LTD, 32 JAMESTOWN RD, LONDON NW1 7BY, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives. Small diameter PTFE grafts are prone to thrombosis and intimal hyperplasia development. Heparin graft coating has beneficial effects but also potential drawbacks. The purpose of this study was to evaluate the experimental efficacy of PEG-hirudin/iloprost coated small caliber PTFE grafts.

Methods. Thirty-six femoro-popliteal ePTFE grafts (expanded polytetrafluoroethylene, diameter 4 mm) were inserted into 18 pigs. Grafts were randomised individually for each leg and grouped for 3 groups. Group 1 consisted of native ePTFE grafts, group II were grafts coated with a polylactide polymer (PLA) without drugs and group III grafts were coated with PLA containing a polyethylene glycol (PEG)-hirudin/iloprost **combination.** The follow-up period was 6 weeks. Patency rates were calculated and development of pseudointima inside the grafts was noted. Thickness of intimal hyperplasia at the distal anastomoses was measured using light microscopy.

Results. Patency rates for group I were 6/9 (67%), for group II 9/10 (90%) and 12/12 (100%) for group III. In groups I and II there was a significant reduction of blood flow proximal to the graft at graft harvest, to 29 +/- 12 and 28 +/- 20 ml/min respectively (both $p < 0.01$ versus preoperative value), whilst in group III blood flow, 99 +/- 21 ml/min, remained at the preoperative level. Subtotal stenosis due to

development of pseudointima was noted in each of the native and PLA coated grafts but not in group III grafts. Intimal hyperplasia at the distal anastomosis was lowest in group III.

Conclusions. The PEG-hirudin/iloprost coating of ePTFE prostheses effectively reduced pseudointima and intimal hyperplasia development and led to superior graft patency.

L27 ANSWER 4 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006381737 EMBASE Phase II evaluation of docetaxel plus exisulind in patients with androgen independent prostate carcinoma. Sinibaldi V.J.; Elza-Brown K.; **Schmidt J.**; Eisenberger M.A.; Rosenbaum E.; Denmeade S.R.; Pili R.; Walczak J.; Baker S.D.; Zahurak M.; Carducci M.A.. Dr. V.J. Sinibaldi, Johns Hopkins Medical Institutions, 550 North Broadway, Baltimore, MD 21205, United States. sinibvi@jhmi.edu. American Journal of Clinical Oncology: Cancer Clinical Trials Vol. 29, No. 4, pp. 395-398 2006.

Refs: 12.

ISSN: 0277-3732. E-ISSN: 1537-453X. CODEN: AJCODI

00000421200608000000013. Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 20060823. Last Updated on STN: 20060823

AB OBJECTIVES: In this phase II study, the **combination** of docetaxel and exisulind (a GMP phosphodiesterase inhibitor) was given to patients with metastatic androgen independent prostate cancer (AIPC) to establish efficacy, assess toxicity, and determine pharmacokinetics of docetaxel administered alone and in **combination** with exisulind. METHODS: Fourteen patients with metastatic AIPC were registered to receive weekly docetaxel for 4 weeks, followed by 2 weeks of rest; repeated up to a maximum of 6 cycles. Exisulind 250 mg was given orally twice a day starting on day 8 of the study and taken continuously. RESULTS: All patients were evaluable for toxicity, response and survival. Grade 3 reversible toxicities included: fatigue, nausea, diarrhea, abdominal pain, rash, syncope, pulmonary edema, deep vein thrombosis, congestive heart failure, and elevations in transaminases, requiring therapy delays and/or dose reductions, or removal from therapy. Only 3 out of 14 patients (21.4%) had a 50% decline in prostate specific antigen (PSA) level that lasted ≥4 weeks; 1 out of 14 patients (7%) had a lymph node response. Median survival was 17.28 months. Docetaxel pharmacokinetics for 11 patients demonstrated mean ± SD clearance values that were similar during week 1 and week 3 when exisulind had been added. CONCLUSIONS: Overall, our trial indicated that the toxicity profile and efficacy of this regimen is unlikely to be substantially better than single agent docetaxel.

L27 ANSWER 5 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006544211 EMBASE Immunosuppressive standards in simultaneous kidney-pancreas transplantation. Schmied B.M.; Muller S.A.; Mehrabi A.; Welsch Th.; Buchler M.W.; Zeier M.; **Schmidt J.**. Dr. B. Schmied, Chirurgische Klinik, Universitat Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany. bruno.schmied@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 44-50 2006.

Refs: 40.

ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 20061122. Last Updated on STN: 20061122

AB Simultaneous pancreas-kidney transplantation is an established procedure for patients with type I diabetes and end-stage renal disease. Continuous advances in the operation techniques with consequent reduction of perioperative morbidity and mortality and the introduction of modern immunosuppressive agents improved not only patients but also graft survival and significantly decreased rejection episodes of both kidney and

pancreas grafts. Availability of a variety of new immunosuppressants in the clinical routine and increasing experience of the transplant specialists allowed further developments of therapeutic schemes with application of induction and maintenance immunosuppressive protocols. In this article, we summarize the current status of immunosuppressive regimens in simultaneous pancreas and kidney transplantation. .COPYRGT. 2006 Blackwell Munksgaard.

L27 ANSWER 6 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006544210 EMBASE The role and value of sirolimus administration in kidney and liver transplantation. Mehrabi A.; Fonouni H.; Kashfi A.; Schmied B.M.; Morath Ch.; Sadeghi M.; Schemmer P.; Encke J.; Sauer P.; Zeier M.; Weitz J.; Buchler M.W.; **Schmidt J.**. Dr. A. Mehrabi, Division of Visceral Transplantation, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany. arianeb_mehrabi@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 30-43 2006.
Refs: 58.
ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061122. Last Updated on STN: 20061122

AB Enormous advancements in visceral transplantation have led to significant improvements in the quality of life of patients. However, despite these developments, the average graft half-life after transplantation has remained almost unchanged and chronic rejection is still considered a major problem. In this regard, more concerns have shifted to factors influencing long-term graft survival, patient survival, and quality of life. To achieve this goal, detrimental effects of immunosuppressive (IS) agents, which have deleterious influence on the quality of life and/or patient survival, should be reduced. In the course of recent years, the transplant community has worked on reducing these side effects by developing new ISs, employing new **combination** regimens, or finding and adjusting optimal dosages and blood level concentrations. Among the IS agents, the antifungal, antitumoral and IS activity of mammalian target of rapamycin (mTOR) inhibitors without nephrotoxicity, have received special attention regarding this new class of IS. Sirolimus (SRL), as the first member of mTOR inhibitors, has been utilized in many clinical trials with respect to its benefit-risk assessment. In our review, the clinical evolution of SRL, as well as the evidence-based clinical benefits of SRL in kidney and liver transplantation (KTx, LTx), are summarized. Various studies of SRL in KTx and LTx have shown that **combination** therapy with SRL will enrich the variety of IS modalities. It also can be regarded as a safe base therapy to which other necessary drugs can be added. In addition to the enhanced acute rejection prophylaxis, and in contrast to the calcineurin inhibitors (CNI) and steroids, this drug solely does not have common side effects such as nephrotoxicity, neurotoxicity, diabetes mellitus and hypertension. Moreover, this agent might diminish vasculopathic processes that mediate chronic allograft nephropathy (CAN). Therefore, by reducing the likelihood of CAN it can decrease the rate of long-term organ failure. One possibly desirable characteristic of SRL is its antiproliferative effect, which could provoke antitumoral or antiatherogenic activity following transplantation. Despite all promising impacts of SRL in organ transplantation, there are some concerns regarding the adverse effects of this drug, for instance dyslipidemia, pneumonitis and wound healing problems. However, the majority of these side effects can be reduced or ceased by careful dose adjustments and correct timing of use. In conclusion, after a decade of both in vivo and in vitro studies on SRL, it can be advocated that SRL is a promising, potent and effective IS agent as it reduces the rate of acute rejection episodes in de novo transplants. It could improve the quality of life, graft and patient survival rate, and achieve excellent outcomes with few adverse effects when wisely used in **combination** with other immunosuppressants. .COPYRGT. 2006

Blackwell Munksgaard.

L27 ANSWER 7 OF 14 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2005:479942 Document No.: PREV200510266527. Cytotoxic activity of cytokine-induced killer cells correlates with expression of SAP and SLAM. Mehrle, Stefan [Reprint Author]; Frank, Susanne; **Schmidt, Jan**; Buchler, Markus W.; Schmidt-Wolf, Ingo G. H.; Marten, Angela. Univ Heidelberg, Dept Surg, D-6900 Heidelberg, Germany. Blood, (NOV 16 2004) Vol. 104, No. 11, Part 2, pp. 55B-56B.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB SAP is a small protein, consisting of a single SH2 domain which is mutant in humans with X-linked lymphoproliferative disease. Patients with XLP are affected by fatal EBV infections and malignant B cell lymphomas. The increased risk for B cell lymphomas is suggested to result from impaired immunosurveillance ofB cell proliferation by T cells. Here, we investigated the role of SLAM/SAP for activation of effector cells with cytotoxic activity (CIK cells), which aregenerated by unspecific stimulation of the T cell receptor and addition of exogenous IL-2 as described previously. The TCR activation on day +1 resulted not only in a short, peak of activated cells, but activation continued and increased in **combination** with IL-2. We observed a striking peak of SLAM (Signaling Lymphocyte Activation Molecule) on day +6 in form of extracellular detectable CD150 as well as at the level of proteins and mRNA. Interestingly, the cytotoxic activity and the amount of SHP-2 protein showed a similar pattern as the parameters mentioned above but were shifted one day. Comparing these data for correlation, we observed a significant correlation between cytotoxic activity and CD150 expression pattern ($P<0.001$) and amount of SLAM protein ($P<0.02$) as well as between amount of SHP-2 protein and SLAM parameters ($P<0.03$). IL-10 secretion did not correlate with any of the parameters investigated. Secretion of Th1/Th2 cytokines was determined using a cytometric bead assay. There was no change in the amount of IL-6 and TNF-alpha. IL-4 was below the detection threshold and IL-2 could not be analyzed due to exogenous addition. IFN-gamma levelsincreased during cultivation, peaked on day +3 and then remained at about 4ng/ml. IL-10 secretion started after stimulation of cells by anti-CD3, peaked onday +3 and then decreased continuously. Between day +6 and day +7. only 0.86 +/- 0.02ng/ml/24hrs/3x 10(6) cells were secreted. In summary, activation of peripheral blood cells with agonistic anti-CD3 **antibody** and exogenous IL-2. as used for generation of CIK cells, results in significant SLAM and SAP activation five days after TCR stimulation. This peak correlates with cytotoxic activity against tumor cells. SLAM expression and binding by SAP seems to beimportant in the activation of cytotoxic effector cells.

L27 ANSWER 8 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2004366326 EMBASE Long-term results of paediatric kidney transplantation at the University of Heidelberg: A 35 year single-centre experience. Mehrabi A.; Kashfi A.; Tonshoff B.; Feneberg R.; Mehls O.; Schemmer P.; Kraus T.; Wiesel M.; Buchler M.W.; **Schmidt J.**. Dr. J. Schmidt, Dept. of Gen. Visc./Transplant Surg., University of Heidelberg, IFN 110, 69120 Heidelberg, Germany. jan_schmidt@med.uni-heidelberg.de. Nephrology Dialysis Transplantation Vol. 19, No. SUPPL. 4, pp. iv69-iv74 2004.
Refs: 23.
ISSN: 0931-0509. CODEN: NDTREA
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20040916. Last Updated on STN: 20040916

AB Background. Kidney transplantation remains the most effective treatment for children with end-stage renal disease. We analysed data from the University of Heidelberg transplant programme to present our results on paediatric kidney transplantations over the past 35 years. Methods. From 1967 to 2003, 354 paediatric kidney transplantations were performed at the

University of Heidelberg. Data were obtained from the paediatric kidney transplantation records consisting of 291 (82%) cadaveric and 63 (18%) living donated transplants. Demographic data, family relationship of the living donors, surgical technique, immunosuppressive drugs, graft and patient survival rates were assessed. Results. The mean age of cadaveric and living donors was 32.0 ± 17.1 and 37.6 ± 7.5 years, respectively. The family relationship of the living donors included the mother in 65% of cases, the father in 31%, and other relatives in 4%. In the last 4 years, the respective mean cold ischaemia time was 1.6 ± 0.5 h for living donated and 13.5 ± 4.1 h for cadaveric donors. The mean age of children who received kidneys from cadaveric and living donors was 11.3 ± 4.5 and 10.4 ± 4.5 years, respectively, with a male to female ratio of 57 to 43%. Overall patient survival rates were 95% after 1 year and 89% after 5 years. The patient 5 and 10 year survival rates for living donor renal transplantations were 95 and 95%, respectively. Graft survival rates improved since 1990 compared with the period prior to 1990: 82.5 vs 56.7% graft survival at 1 year and 82.5 vs 50% after 5 years (P = 0.03). Comparing the operating technique in a subgroup of our patients that received the same immunosuppressive regimen, anastomoses with the aorta and vena cava (51%, n = 31) were associated with a graft survival of 86.6 and 83.3% after 1 and 5 years, whereas anastomoses with iliac vessels (49%, n = 30) were associated with a graft survival of 55.8 and 51.6% after 1 and 5 years, respectively (P = 0.01). Conclusions. There has been a gradual improvement in our paediatric kidney transplantation results over time. Living donor paediatric kidney transplants have higher patient and better graft survival rates than cadaveric donor kidney transplants. Using the aorta and inferior vena cava for graft anastomosis, utilizing newer immunosuppressive drugs and implementing living kidney donation have positively affected the results of our paediatric kidney transplantations.

L27 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 1

2003358443. PubMed ID: 12891121. Inducible nitric oxide synthase is present in human abdominal aortic aneurysm and promotes oxidative vascular injury. Zhang Jian; **Schmidt Jan**; Ryschich Eduard; Mueller-Schilling Martina; Schumacher Hardy; Allenberg Jens Rainer. (Third General Surgery Department, First Affiliated Hospital, China Medical University, Shenyang 110001, China.. jianzhang_cmu@yahoo.com.cn) . Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, (2003 Aug) Vol. 38, No. 2, pp. 360-7. Journal code: 8407742. ISSN: 0741-5214. Pub. country: United States. Language: English.

AB OBJECTIVE: Nitric oxide (NO), catalyzed by inducible NO synthase (iNOS), may be important in the pathophysiologic characteristics of many vascular diseases. Although there is indirect evidence to support the presence of iNOS in abdominal aortic aneurysm (AAA) in human beings, no definitive study has confirm this finding. The present study was designed to assess expression of iNOS in AAA in human beings. Furthermore, the activity of iNOS and the oxidative vascular injury initiated by iNOS were assessed with detection of nitrotyrosine, which is a marker indicative of formation and activity of the NO-derived oxidant peroxynitrite. METHODS: We studied 25 patients with AAA and 10 patients with normal abdominal aortas. In situ hybridization and immunohistochemistry were used in tissue sections to localize iNOS messenger RNA (mRNA) and protein. Double staining with a **combination** of in situ hybridization and immunohistochemistry was used to simultaneously demonstrate iNOS mRNA expression and its cellular localization. The presence of peroxynitrite was indirectly assessed with immunostaining with anti-nitrotyrosine **antibodies.** RESULTS: In situ hybridization and immunohistochemistry confirmed the presence of iNOS in media and adventitia of AAA in all 25 patients. Specific cell markers identified iNOS mRNA-positive cells mainly as T and B lymphocytes, macrophages, and smooth muscle cells. Positive immunostaining for nitrotyrosine was present in macrophages and smooth muscle cells. Normal abdominal aorta demonstrated virtually no iNOS or nitrotyrosine

expression. CONCLUSION: Stimulated expression of iNOS is associated with degeneration of AAA in human beings, and the activity of this enzyme under such conditions preferentially promotes formation and activity of peroxynitrite and further contributes to oxidative tissue and cellular injury in AAA. This may be important in the pathogenesis of AAA.

L27 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
2002:539555 Document No. 137:108304 Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting **antibodies** and angiogenesis inhibitors for treating cancer and metastasis. Goodman, Simon; **Kreysch, Hans-Georg** (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2002055106 A2 20020718, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP15241 20011221. PRIORITY: EP 2001-100507 20010109.

AB The invention relates to a **combination** therapy for the treatment of tumors and tumor metastases comprising administration of receptor tyrosine kinase antagonists/inhibitors, especially ErbB receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said **combination** of antagonists/inhibitors, such as chemotherapeutic agents and or radiation therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone.

L27 ANSWER 11 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
1998217602 EMBASE Hepatitis C virus dynamics in vivo: Effect of ribavirin and interferon alfa on viral turnover. Zeuzem S.; **Schmidt J.M.**; Lee J.-H.; Von Wagner M.; Teuber G.; Roth W.K.. Dr. S. Zeuzem, Medizinische Klinik II, Zentrum der Inneren Medizin, Klin. Johann Wolfgang Goethe-Univ., Theodor-Stern-Kai 7, D-60590 Frankfurt a.M., Germany.
Hepatology Vol. 28, No. 1, pp. 245-252 1998.
Refs: 36.
ISSN: 0270-9139. CODEN: HPTLD
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 19980904. Last Updated on STN: 19980904

AB Treatment of patients with chronic hepatitis C with recombinant interferon alfa (rIFN-α) can cause a decrease of serum transaminases and hepatitis C virus (HCV) RNA. Recent trials evaluating **combination** therapy of IFN-α and ribavirin suggested a potential synergistic effect. From serial measurements of serum HCV RNA concentrations following treatment-induced perturbation of the balance between virus production and clearance, we compared the antiviral efficacy of both IFN-α alone and IFN-α in **combination** with ribavirin. Chronically HCV-infected patients were treated with either 3 x 3 MU or 3 x 6 MU rIFN-α per week or 3 x 6 MU rIFN-α plus 14 mg/kg of body weight ribavirin per day The time-dependent HCV RNA concentrations during antiviral treatment were analyzed by iterative least- squares regression. After initiation of antiviral therapy, HCV RNA declined exponentially below the detection limit of the reverse-transcription polymerase chain reaction assay (1,000 HCV RNA molecules per milliliter) in 10 of 26 (39%), 10 of 19 (53%), and 10 of 18 patients (56%) treated with 3 x 3 MU, 3 x 6 MU rIFN-α without and with ribavirin, respectively Viral clearance from serum was faster in patients treated with 3 x 6 MU rIFN-α ($t(1/2) = 0.23 \pm 0.15$) compared with patients treated with 3 x 3 MU

rIFN-α per week (0.67 ± 0.36 days) (P < .004). However, half-lives of viral clearance were similar in patients treated with rIFN-α or rIFN-α plus ribavirin. For virus release from infected hepatocytes, absence and presence of ribavirin yielded half-lives of t(1/2) = 2.54 ± 2.10 and t(1/2) = 1.99 ± 1.70, respectively, indicating that ribavirin does not significantly inhibit HCV production. In conclusion, the data of the present study indicate that higher rIFN-α doses accelerate viral clearance from serum. Ribavirin (14 mg/kg/d), however, lacks synergistic antiviral effects in the treatment of chronic hepatitis C with 3 x 6 MU rIFN-α per week.

L27 ANSWER 12 OF 14 MEDLINE on STN

94350639. PubMed ID: 8071057. Effect of corticosteroids, cyclosporin A, and methotrexate on cytokine release from monocytes and T-cell subsets. **Schmidt J**; Fleissner S; Heimann-Weitschat I; Lindstaedt R; Pomberg B; Werner U; Szelenyi I. (Department of Pharmacology, ASTA Medica AG, Frankfurt/Main, Germany.) Immunopharmacology, (1994 May-Jun) Vol. 27, No. 3, pp. 173-9. Journal code: 7902474. ISSN: 0162-3109. Pub. country: Netherlands. Language: English.

AB Corticosteroids are the most effective drugs in the management of asthma. However, because of their known side effects and the existence of corticosteroid-resistant patients, there is a need for substitute medications in asthma therapy. Using cell lines, in the present study, the two corticosteroids dexamethasone (Dex), and beclomethasone (Bec), as well as the immunosuppressant cyclosporin A (CsA), and the antimetabolic drug methotrexate (Mtx) were examined in their effect on release of immunoreactive IL-1 beta, IL-2, IL-4, IL-5, and IL-8. THP-1 cells served as a test model for monocytes secreting IL-1 beta and IL-8 upon stimulation by lipopolysaccharide. Jurkat cells were used as a test model for TH1-type T-cells and were stimulated for IL-2 release with a **combination** of phytohemagglutinin and phorbol myristate acetate. Representing TH2-type T-cells, D10.G4.1 cells challenged by anti-CD3-mAb produced IL-4, and IL-5. Considerable qualitative and quantitative differences in the relative efficacy of the test compounds were found. Following IC50 values (nmol/l) of the test compounds were estimated (IL-1 beta/IL-8/IL-2/IL-4/IL-5): Dex (10.8/35.7/ > 10,000.0/5.1/4.1), Bec (30.9/102.2/8591.4/0.6/0.4), and CsA (318.7/6211.2/2.3/68.2/237.9). Mtx in concentrations up to 10,000.0 nmol/l was completely inactive. It can be concluded that corticosteroids show another inhibition pattern than CsA: corticosteroids affect mainly TH2-type T-cells, while CsA primarily inhibits the TH1-type T-cell response.

L27 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

1982:102117 Document No. 96:102117 Monoclonal **antibodies** to the human leukocyte interferons and their use for interferon purification and a quantitative interferon assay. Staehelin, Theophil; Takacs, Bela; Durrer, Brigitte; **Schmidt, Joerg**; Stocker, John; Miggiano, Vincenzo; Staehli, Christian; Hobbs, Donna S.; Kung, Hsiang Fu; Pestka, Sidney (Pharma Res. Div., F. Hoffmann-La Roche and Co. Ltd., Basel, CH-4002, Switz.). Symposia of the Giovanni Lorenzini Foundation, 11(Monoclonal Antibodies Dev. Immunoassay), 79-85 (English) 1981. CODEN: SGLFD9. ISSN: 0166-1167.

AB A collection of 12 monoclonal **antibodies** to human leukocyte interferon is discussed. The **antibodies** comprise 4 different heavy- light-chain isotype **combinations. Antibody** -binding and interferon-neutralization results suggest that at least 3 distinct epitopes of human leukocyte interferons can be recognized and defined by these monoclonal **antibodies.**

L27 ANSWER 14 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

80223022 EMBASE Document No.: 1980223022. Biochemical methods in the treatment of sexual disorders. **Schmidt Jr. C.W.**. Dept. Psychiat., Baltimore City Hosp., Baltimore, Md. 21224, United States. Psychiatric Clinics of North America Vol. 3, No. 1, pp. 189-199 1980.

CODEN: PCAMDG
Pub. Country: United States. Language: English.
Entered STN: 911209. Last Updated on STN: 911209
AB Future biochemical treatment of sexual disorders will follow developments in brain neurochemistry and will bring about **combinations** of psychopharmacologic methods. However, the success in creating multimodal treatments will require interdisciplinary collaboration.

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